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Hyperplastic polyps and sessile serrated adenomas: the differential diagnosis dilemma

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Serrated polyps (SPs) are a heterogeneous family of polyps with distinct molecular underpinnings, clinicopathologic features and a varied capacity of malignant potential. They are new target lesions for endoscopists and pathologists, often underestimated and misdiagnosed. Due to their similar endoscopic and anatomopathologic characteristics a diagnostic overlap between hyperplastic polyps (HPs) and sessile serrated adenomas (SSAs) has been reported; nevertheless it is of utmost importance to correctly distinguish them since they have different malignant potential. The aim of this study was to evaluate the misdiagnosis rate of SSAs as HPs during a 8 years period (2006—2013) and the association between SSAs and other colorectal lesions. **Methods:** a retrospective, double blinded analysis of histologic specimens of all HPs diagnosed from January 2006 to December 2013 at Florence University Hospital was performed. The hospital database was consulted looking for association between SPs and other colorectal lesions. **Results:** after specimens revision of 2412 HPs the diagnosis from HP to SSA was changed in a 4,6% of cases (p=0,04). The change of diagnosis was assumed only if a 100% interobserver agreement was reached. SSAs resulted to be significantly more associated with other colorectal lesions (synchronous or metachronous) when compared with traditional serrated adenomas (TSAs) and mixed polyps (MPs). **Conclusions:** SSAs are more frequent than previously reported and are often misclassified as HPs (diagnostic overlap). The correct diagnosis of SSAs is important because they are the serrated polyps associated with a more rapid development of cancer and most associated with other colorectal lesions and other neoplasia.

Keywords: colorectal neoplastic lesions, hyperplastic polyps, sessile serrated adenomas, malignization, cancer, differential diagnostics.

The 1st serrated lesion to be described was the traditional serrated adenoma, defined by Longacre and Fenoglio Preiser in 1990 as «polyp with the architectural but not the cytologic features of Hyperplastic Polyp (HP)» [1]. Six years later Torlakovic and Snover defined the «serrated adenoma» as a distinct type of polyp that differed from the closely resembling hyperplastic polyp [2]; the term «sessile serrated adenoma» was so introduced. From that time many efforts have been made to characterize these lesions from an pathological, molecular and endoscopic point of view. Serrated colon polyps area group of heterogeneous lesions histologically characterized by glandular serration (ie, a saw-tooth folding of colonic crypt epithelium). The World Health Organization classified them as: Hyperplastic Polyps (HPs), Sessile Serrated Adenoma/Polyp (SSAs), Traditional Serrated Adenomas (TSAs), Mixed Polyps (MPs) and according to literature data they are the 36% of all colonic polyps [3]. While TSAs and MPs have always been diagnosed as adenomatous polyps and like them treated and surveilled, HPs and SSAs were once all diagnosed as HPs (diagnostic overlap), the differential diagnosisis difficult also for the pathologist but of significant importance since they have completely different anatomopathological, molecular, endoscopic features and as a consequence of that different malignant potential and follow-up. Exception made for HPs, the other serrated lesions have a malignant potential and follow a different pathway of carcinogenesis to the traditional «adenoma-carcinoma sequence». TSAs are more frequently KRAS mutated, but they can also be BRAF mutated [4, 5]; they follow the so called «alternative pathway» that leads to cancers that have similar features to the onesoriginating from the traditional adenomas: CIMP low and microsatellite stable [5—7]. SSAs are associated with BRAF mutations and follow the so called «serrated pathway» that leads to cancers that are CIMP high and microsatellite instable and are very similar to the ones seen in Lynch syndrome [6, 8—11]. The progression from a SSAto cancer is more rapid once that dysplasia arises [12]. A number of studies have reported that SSAs are associated with an increased risk of synchronous and metachronous neoplasia, including both advanced adenomas and cancer [13—18].

The aim of this study was to evaluate the misdiagnosis rate of SSAs as HPs during a 8 years period (2006—2013) and the association between SPs and other colorectal lesions.

We decided to focus on SSAs since they represent, in our opinion, the subtype of serrated lesion of most interest both for pathologists and endoscopists because of

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many reasons: they are frequently misdiagnosed as HPs, differently from HPs they have a malignant potential with a pathway to cancer that is similar to the one of Lynch syndrome, they are difficult to detect and because of this they are thought to be associated to up to 50% of interval colorectal cancer, they are the lesions found in serrated polyposis syndrome and their number is correlated to the risk of developing a colorectal cancer and they have been found to be associated with other colorectal lesions with a higher incidence than the other serrated lesions.

Methods

All SPs diagnosed from January 2006 to December 2013 at Florence University Hospital were included in the study. Histopathologic diagnosis was made applying the WHO 2010 classification.Criteria used for the definition each lesion are shown in Table 1. Hematossilin-Eosin slides of each HP diagnosed in the period 2006—2013 were reviewed in a double-blinded analysis by expert pathologists for colon and rectum whose interest is focused on serrated lesions to see how many SSAs were misclassified as HPs. The diagnosis has been changed from HP to SSA only for those lesions with a 100% interobserver agreement. The hospital database was consulted looking for patients clinical history, each synchronous or metachronous colorectal lesion (premalignant or malignant) were recorded. In the analysis of the association between SPs and other colorectal lesions we considered only those SPs with a malignant potential: SSAs and the group TSAs + MPs.

Statistical analysis

Proportion of diagnosis changed and its confidence interval is reported. In order to assess association between categories variable chi-square test was used.

Results

Over the 8 year period 12 842 colorectal polyps were diagnosed, of these 2557 (20%) were serrated lesions. After the double-blinded specimen revision by the pathologists the diagnosis from HP to SSAchanged in a 4,6% of cases (p=0,04) **(table 2)**.

One hundred two SSAs (52%) resulted to be associated with other colorectal lesions, of these 35 (18%) were associated with colon cancer, 49 (25%) with adenomas with high grade dysplasia and 18 (9%) with other serrated lesions (table 3). A statistically significant difference in the association with other colorectal lesions was found between SSAs and the group TSAs/MPs **(table 3)**.

Most of SSAs associated wih colon cancer were >5 mm in diameter **(table 4)**.

Discussion

In this retrospective study we aimed to evaluate the misdiagnosis rate of SSAs as HPs and the association between SSAs and other colorectal lesions in a cohort of patients who underwent colonoscopy and subsequent polypectomy for any reason at a tertiary center. We focused on SSAs because in our opinion they are the class of serrated polyps of main interest, because of their biology and association to cancer. In our experience serrated polyps were 20% of all colonic polyps, HPs were the most common (94,3% of serrated polyps), an incidence even higher ofthat reported by the literature [19, 20]. We hypothesized that this can be the result of a misclassification of some SSAs as HPs due to the diagnostic overlap, most of them occurring in the first years of the period we examined when the knowledge about these lesions was still limited. This would also explain our lower incidence of SSAs (3,4% of serrated polyps) to that reported by the literature (10—25% of serrated polyps) [8, 21]. After the double blinded specimen review by expert pathologists we reported a decrease in the incidence of HPs from 94,3% to 90% of all serrated polyps (18% of all colorectal polyps) and an increase of SSAs from 3,4% to 4,3% of all serrated polyps (0,8% of all colorectal polyps). Our data support the findings of previous studies that reported ahigh frequency of misclassification of SSAs as HPs even in tertiary centers [22, 23].

At the present in our clinic every time that a pathologist suspects a serrated polyp asks for a second and then a third opinion if necessary. The incidence of TSAs in our

***Table 1*. WHO 2010 serrated polyps classification**

Sign	Hyperplastic polyps	Sessile serrated adenoma/polyp	Traditional serrated adenoma
Microscopy	Elongated crypsts Serration in the top half or top third of the crypts Small, uniform, basally placed nuclei No cytological atypia or architectural dysplasia	T- and L-shaped crypts above the muscolaris mucosae Branching of the crypts in the lower third of the mucosa	Citologic dysplasia Diffuse eosinophilic cytoplasm Ectopic crypt formation Prominent serration Penicillate nuclei
Proliferation's index	Normal	Asymmetrical distribution	Increased
Degenerative potential	No	Yes	Yes

Table 2. **Polyps diagnosed in the period 2006—2013 at Florence University Hospital (a tertiary center)**

Sign	*n*	% of serrated/conventional	% of total#
Serrated polyps	*2412*/2301***	94,3*/90**	18,7*/18**
Hyperplastic	*89*/111***	3,4*/4,3**	0,6*/0,8**
Sessile serrated adenoma/polyp	*p*=0,04***		
Traditional serrated adenoma	45	1,7	0,3
Mixed	11		0,1
Total	2557	0,4	20
Conventional adenomas			
Tubular	5372	52,4	42
Tubulo-villous	4876		38
Villous	37	47,6	0,2
Total	10 285	0,36	80

* — before specimen revision; ** — after specimen revision; *** — 95% Confidence Interval 0.0380-0.0552.

Table 3. **Association between serrated polyps and other intestinal lesions *HGD=high grade dysplasia***

Sign	SSA, abs./% (*n*=197)	TSA+MP, abs./% (*n*=56)	Total, abs./% (*n*=253)	*p*
Colorectal cancer	35/18	6/11	41/16	<0,001
Adenoma with HGD	49/25	4/7	53/21	
Other serrated lesions	18/9	3/5	21/8	
	102/52	13/23	115/45	

study is a little bit higher but however in agreement with that reported by the literature (1%) [19, 21].

Our data support the findings of previous studies that report an association between serrated lesions and other colorectal lesions, including both advanced adenomas and cancer [13—17]. The association of serrated lesions with conventional adenomas may seem strange given their divergent biology, some experts have suggested that some of the synchronous «advanced adenomas» may be misclassified dysplastic SSAs which can be difficult to distinguish from conventional adenomas with villous features and/or high grade dysplasia [24].

Due to the higher prevalence of SSAs in the right colon pancolonoscopy should always be included in a screening program and a good quality colonoscopy, as well as a clean colon, are key quality indicators of utmost importance for the detection of these lesions [25]. For this reason we do not agree with the proposal of some authors to perform only sigmoidoscopy in screening programs [26—28].

The current guidelines from the American Society of Gastrointestinal Endoscopy (ASGE) and European Societies for Gastrointestinal Endoscopy (ESGE) advocates the standard 5 years surveillance period for low risk lesions (SSA <10 mm and without dysplasia) in patients without serrated polyposis syndrome. Patients with larger SSAs or with dysplasia should have their colonoscopy repeated in 3 years time [29, 30]. The major problem is that these guidelines rely upon the assumption that the serrated lesions are detected and resected adequately, which is not always the case. Since the serrated pathway is more rapid once that dysplasia arises, a misdiagnosis/undetection/not adequate resection can lead to interval colon cancers.

Table 4. **Size of serrated polyps associated with colon cancer**

Size	SSA, abs./% (*n*=35)	TSA+MP, abs./% (*n*=6)
<5 mm	4/11	2/33,3
5—10 mm	13/37	2/33,3
>10 mm	18/51	2/33,3

Conclusions

This study gives a further contribution in the definition of the epidemiology of serrated polyps that are a heterogeneous family of polyps with distinctmolecular underpinnings, clinicopathologic features and a varied capacity of malignant potential. They are new target lesions for endoscopists and pathologists, often understimated and misdiagnosed. SSAs are 2nd to HPs in frequency and are often misclassified as HPs (diagnostic overlap). In our experience SSAs are the most associated with other colorectal lesions.

A good quality screening colonoscopy as well as detection and adequate resection of SSAs is of utmost importance since there are probably the main responsible of interval cancer.

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