ORIGINAL ARTICLE

Location and Size are Useful Features in Diagnosing Sessile Serrated Adenoma/Polyp

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ABSTRACT

Introduction: According to the predefined 2010 World Health Organisation criteria, serrated colonic polyps (SCP) are pathologically classified into hyperplastic polyp (HP), sessile serrated adenoma/polyp (SSA/P) with or without cytological dysplasia and traditional serrated adenoma (TSA). Sessile serrated adenoma/polyp is acknowledged as a precursor of colorectal carcinoma through the serrated neoplastic pathway. Hyperplastic polyps display similar histological features to SSA/P, in comparison to other types of SCP. It is noteworthy to discriminate between HP and SSA/P, since only the latter has a malignant potential. **Method:** A total of 198 cases of SCP were identified and the slides were reexamined and reclassified accordingly. Analysis on the proportion of SSA/P among SCP and underdiagnosed cases of SSA/P was performed. The association between SSA/P and non-SSA/P with demographic data and colonoscopic findings were also studied. **Results:** From the 198 cases of SCP, 164, 29 and five cases were reclassified as HP, SSA/P and TSA respectively. Sixteen cases of SSA/P were underdiagnosed as HP. From among 29 cases of SSA/P, the majority were ≥ 65 years old (17; 58.6%), male (21; 72.4 %) and Chinese (17; 58.6%). Most of the SSA/P (16; 55.2 %) were located in the right colon and measured ≥ 10mm (9; 31%) in size. Location (p=0.004) and size (p=0.013) of the colonoscopic findings were significantly associated with SSA/P. **Conclusion:** Underdiagnosed cases of SSA/P among HP were identified most likely because of the resemblance of their histological features. The location and size of SCP may suggest the probability of SSA/P.

Keywords: Sessile serrated adenoma, Serrated polyp, Colorectal carcinoma, Colonic polyp

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INTRODUCTION

Colorectal carcinoma (CRC) is the third most common cancer and the fourth leading cause of all cancer-related mortality worldwide (1). In the context of Malaysia, CRC is the second most common cancer among Malaysian residents after breast cancer, and followed by lung cancer. It is the most common cancer among male residents. The incidence of colorectal cancer increases with age, and is the highest among the Chinese population for males and females (2).

Most CRCs develop through the classic adenoma-carcinoma sequence and the remainder evolve via either the hypermutant or ultramutant pathway. The most frequent genetic changes in the conventional colorectal adenoma-carcinoma pathway are 84% by chromosomal instability pathway (alteration to *APC, KRAS, TP53, SMAD4* and *PIK3CA*), 13% by the microsatellite instability (MSI) hypermutant pathway (i.e. mismatch repair genes *MLH1* and *MSH2*) and 3% by ultramutant pathway (i.e. Polymerase ε / *POLE*). Adenomatous polyposis coli (*APC*) alterations are the most inactivating mutations that are found early in the sequence and initiates the formation of adenoma (3).

Screening colonoscopy with polypectomy is a useful practice to lower the incidence and in turn the fatality rate of CRC. It suggests that the age adjusted incidence of distal (left) colon cancer has steadily dropped in the United States from 1976 to 2005 but stays constant for the incidence of right-sided colon cancer. It is likely partly due to underdiagnosed sessile serrated adenoma/polyp (SSA/P).

Since the past two decades, nearly all colorectal polyps were categorised into two main groups, namely hyperplastic polyp (HP) and adenoma. Longacre and Fernoglio-Preiser in 1990, observed that some of the

serrated polyps have comparable morphological features to both conventional adenomas and HP (4). Since then, the term traditional serrated adenoma (TSA) has been used.

According to the World Health Organization (WHO) classification of tumour of the digestive system in 2010, serrated colonic polyps (SCPs) are divided into three main categories which are typical HP, SSA/P with or without cytological dysplasia and TSA (5). Hyperplastic polyps are thought to have no malignant potential whereas SSA/P, over the decades, has been recognized as an important precursor of CRC through the serrated neoplastic pathway. The prevalence of SSA/P ranges from 0.1%-14.7% of all colorectal polyps, and has been underdiagnosed for years (6). Similar to SSA/P, TSA is thought to be a premalignant polyp.

Pathologists often encounter problems during the classification of these three different types of serrated polyps, primarily due to their histology overlaps and terminology. A study conducted by Gill et al. (2013) revealed that 30-64% of right-sided polyps which were first diagnosed as HP, were then reclassified into SSA/P. Although it is difficult to classify some of the colonic polyps, several studies among pathologists on the reproducible histological diagnosis of SSA/P by light microscopic diagnosis were carried out and revealed a moderate-to-good agreement in the classification (7).

The latest WHO classification of tumours of the digestive system in 2019 has revised the classification and pathogenesis of serrated lesions of colorectum. SSA/Ps are newly termed as sessile serrated lesions (SSL). One of the reasons is because not all polyps that fall under this category are polypoid. Colorectal serrated lesions and polyps are newly classified into HP; microvesicular type (MVHP) and goblet-cell rich type (GCHP), SSL, SSL with dysplasia (SSLD), TSA and serrated adenoma, unclassified. Unclassified serrated adenoma is the category where the dysplastic serrated polyps are difficult to classify as either TSA or SSLD (3). However, the morphological features for all of the serrated lesions remain the same as in the previous classification.

Thirty percent of all CRCs arise via the serrated neoplasia pathway. SSA/P or SSL and TSA are known as precursors to cancer. The serrated pathway involves a sequence of genetic and epigenetic alterations that lead to the development of sporadic carcinoma with hypermethylation with or without microsatellite instability (MSI). Activating mutations of either *BRAF* (in MVHP, SSL and TSA) or KRAS (in GCHP and TSA) are thought to initiate the development of serrated polyps (3).

Hyperplastic polyp

Clinical features

Hyperplastic polyp is very common compared to other types of SCP. It is small in size, usually less than 5mm. This polyp is usually located in the left colon, particularly the distal colon and rectum. According to endoscopic findings, HP is frequently identified by their symmetrical, smooth and pale appearance and tends to flatten with air insufflation.

Pathological Features

Microscopically, HP displays straight elongated crypts with a serrated architecture involving the upper half of the crypts (8), devoid of cellular atypia and exhibiting bland looking, uniform and small nuclei.

Sessile Serrated Adenoma/Polyp

Clinical features

The prevalence of SSA/P is predicted 1% to 16% from colonoscopy. They are typically flat or slightly elevated, and over 10mm in size. They are located preferentially in the proximal colon. The lesion has a similar colour to the surroundings where it is often being coated by stool or bile salts producing a green or yellow mucus cap (6). In cases of multiple serrated colonic polyps, serrated polyposis syndrome (SPS) need to be excluded. This syndrome, previously known as hyperplastic polyposis syndrome, is associated with increased risk of CRC. According to the classification by the WHO in 2010 (5), SPS is defined by meeting at least one of the following three criteria: 1) More than five serrated polyps above the sigmoid colon with two or more polyps, being larger than 10mm; 2) Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first degree relative with SPS; and 3) More than 20 serrated polyps of any size throughout the colon. Serrated polyposis syndrome has an equal gender distribution, with a median age between 44 to 62 years at diagnosis, ranging from 10-90 years. The polyps are sessile or flat, with typically sized <1cm. Polyps that are >1 cm mostly reside in the proximal colon. The definite risk of CRC in SPS is obscure.

Pathological Features

SSA/P is larger than HP and commonly occurs in the proximal (right) colon. Microscopically, it is characterised by a jagged, disorganised and distorted crypt growth pattern, which may lead to the diagnosis. The crypts serration involves the entire length, including the bottom part, which helps to differentiate from HP. The crypts have distended or irregularly branched bases with a horizontal extension, making an L or inverted T shapes. These features help to distinguish SSA/P

from other serrated polyps (6). In a superficial biopsy or electrocautery artefacts from endoscopic resection, these features are difficult to ascertain, making it challenging to differentiate SSA/P from HP. The basal half of the crypts often contains numerous serration, mature goblet and mucinous cells (10). It is not unusual to see crypts herniation through the muscularis mucosa resulting in pseudoinvasive or inverted growth patterns, which can also be seen in HP. Hence this feature is not pathognomonic for SSA/P. The crypts are lined by columnar secreting cells, and have less eosinophilic cells as compared to TSA.

According to the WHO's classification in 2010, at least three crypts or two adjacent crypts should be present for the diagnosis of SSA/P. Moreover, according to the latest 2019 WHO classification, the presence of at least one of the above crypt features defines architecturally distorted crypts. Recent studies mentioned that the presence of ≥ 1 unequivocal architecturally-distorted serrated crypts is sufficient for a diagnosis of SSA/P or SSL. The American Gastroenterology Association also stated that only one crypt exhibiting the distinctive characteristics of SSA/P is enough for a diagnosis to be made (6). The difference in making a diagnosis between WHO and the American Gastoenterology Association prompts a significant impact on SSA/P prevalence. According to Bettington et al. (2015) (11), the proportion of SSA/P among all the polyps investigated increased from 12.1% to 14.7% when using 2010 WHO and the American Gastroenterology Association criteria respectively.

Some serrated lesions might have mixed features of both MVHP and SSA/P. These lesions are at times described as features of advancement of MVHP to SSA/P. However, MVHP-like features could merely be part of the SSA/P histological spectrum (9). Problems arise when a polyp with predominantly MVHP morphology coexists with only a few, or sometimes a single, irregular, hyperdistended and distorted crypt, as present in SSA/P (12). The presence of at least one unequivocal distorted, distended and/or horizontal branching gland, especially if associated with inverted maturation, is adequate for SSA/P to be diagnosed (13) .

A recent study indicated that SSA/P with conventional adenoma-like dysplasia, tubular or tubulovillous, showed progression towards carcinoma. "Preliminary studies demonstrated that some portion of these lesions exhibit inactivation of mismatch repair gene MLH1; while the dysplastic areas often demonstrate microsatellite instability" (9 p5). This used to be referred to as mixed hyperplastic/adenomatous polyps, but the terminology is discouraged as it does not represent progression of SSA/P to carcinoma. Furthermore, the dysplastic parts have distinctive molecular characteristics that are different from conventional adenoma (9).

Traditional Serrated Adenoma

Clinical features

Traditional serrated adenoma is the least common among all three types of SCP (14). The prevalence of TSA is 0.6%-2.3%, with the usual location being in the distal colon (6,15). The size is significantly larger than HP and SSA/P, and grossly appears to be pedunculated. The features of pedunculated and larger-sized polyps make it easier to be detected.

Pathological Features

Microscopically, TSA shows a complex and distorted tubulovillous or villous configuration. It has a characteristic ectopic crypt formation where there is a budding of proliferative crypts perpendicular to the long axis of the villous structure of TSA. The crypts are lined by columnar cells with abundant eosinophilic cytoplasm and elongated nuclei with dispersed chromatin patterns. Histological features of conventional adenoma-like dysplasia and serrated dysplasia can be seen in TSA (9, 16).

Individuals with SSA/P tend to harbor synchronous adenoma, HPs, and other SSA/Ps (17,18). Both large and/or proximal serrated polyps are at a high risk of synchronous advanced conventional neoplasm (19). Serrated lesions with a size ≥ 10mm, multiple or located in the proximal colon, are more likely to be SSA/P, and are strongly associated with synchronous cancer (20). "MSI-high cancers are more prone to be accompanied by serrated lesion than microsatellite stable cancer" (9 p9). It can be concluded that SSA/P is associated with an increased risk of metachronous cancer.

Rex et al. (2013) recommended to the complete removal of all serrated lesions, except in cases of diminutive sigmoid or rectal lesions (9). Multiple small lesions (<5mm) in the sigmoid or rectum which have a serrated appearance should be taken for histological evaluation, and a complete resection is not required. In terms of surveillance of post endoscopic resection, surveillance intervals are currently in accordance with features of serrated lesions that are associated with advance neoplasia. These features include proximal colon location, increase in number and large size of serrated lesions and SSA/P or TSA (6). Another study has suggested that for sessile serrated polyp <10mm in size with no dysplasia, the surveillance interval is five years. Meanwhile for sessile serrated polyps at least 10mm in size, SSA/P with dysplasia or TSA, the surveillance interval is 3 years. In serrated polyposis syndrome,

the surveillance interval is 1 year. For HP in rectum or sigmoid with a size of <10mm, the surveillance interval is 10 years (21).

MATERIALS AND METHODS

This study was conducted in a government-based hospital in Malaysia. It involved a cross sectional study using retrospective data and random sampling of SCP cases from January 2014 to June 2017.

The slides of cases with the previous diagnosis of HP, SSA/P and TSA were collected and reviewed by two independent pathologists according to the predefined 2010 WHO criteria. In instances where there was discrepancy in the interpretation, the slides were reviewed together by the pathologists to reach a consensus agreement. Validity and reliability of the histopathology reporting in this hospital were according to their Standard Operating Procedure (SOP) and the Histopathology unit was involved in the external quality assurance programme, which is the Royal College of Pathologist of Australasia (RCPA).

All results were analysed using the standard statistical software package, IBM SPSS statistics version 23.0. A Fisher Exact test was used to analyse the association between SSA/P and non SSA/P with demographic data as well as colonoscopic findings. A p-value <0.05 was considered statistically significant.

RESULTS

This study involved a total of 198 cases of SCP, comprising 182 cases of HP, 13 cases of SSA/P and three cases of TSA, diagnosed from January 2014 to June 2017. After the slides were thoroughly reviewed, 16 cases of SSA/P and two cases of TSA were detected to be underdiagnosed as HP, yielding a new total of 29 cases of SSA/P and five cases of TSA (Table I). Fig. 1 depicts the classical histopathological features of SSA/P.

Table I : Distribution of cases according to types of serrated colonic polyp, before and after review.

Types of serrated colonic polyps	n=198 (%)	
	Before review	After review
HP	182 (91.9)	164 (82.8)
SSA/P	13 (6.6)	29 (14.6)
TSA	3 (1.5)	5 (2.5)

HP= Hyperplastic polyp
SSA/P= Sessile serrated adenoma/ polyp
TSA= Traditional serrated adenoma

From among the 29 reviewed cases of SSA/P, the majority was male (72.4%) with an age ranging between 31 to 81 years old (mean age was 65.8 years old). As for race distribution, the Chinese population was predominant (58.6%), followed by Malay (40%)

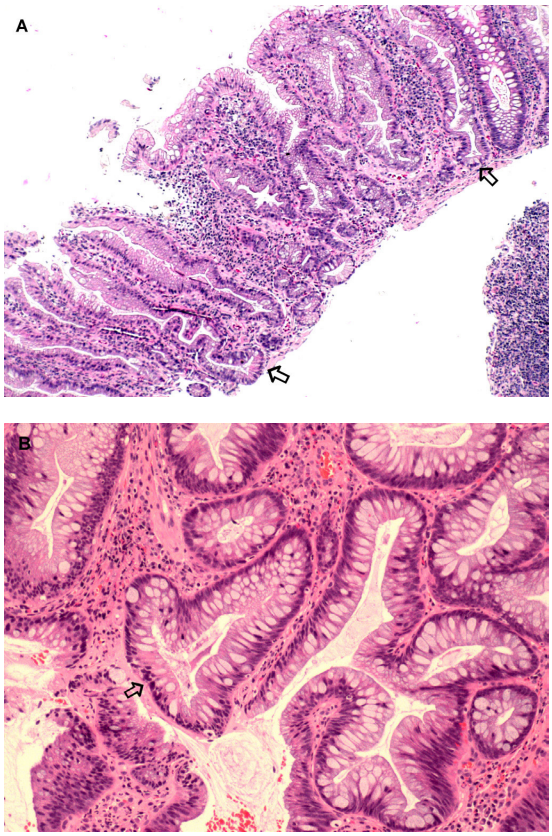

Figure 1 : Sessile serrated adenoma/polyp.
A: Full length serration of the crypts with slight lateral dilatation of the basal part (arrow) (x40).
B: Distorted and lateral dilatation of the crypts at the base forming an inverted T (arrow) (x100).

and Indian (10.3%). As for the location, 16 cases (55.2%) were mostly located in the right colon, while 13 (44.8%) in the left colon. For the size, the majority, 9 cases (31%) of SSA/P measured 10mm or more; while two cases (6.9%) measured less than 10mm. There were 18 cases (62.1%) with missing data.

Statistical analysis indicated significant associations between SSA/P and non-SSA/P with two colonoscopic findings, namely, location (p=0.004) and size (p=0.013). In contrast, no significant association was detected with all the demographic data (Table II).

DISCUSSION

Among the SCP, HP is the most common type of polyp compared to SSA/P and TSA. TSA is far less common than SSA/P (6,14,15). Population-based studies have shown that at least 40% of adults harbor at least a type of SCP (16,19,20). Hyperplastic polyps represent almost 70-90% of serrated colonic polyp, followed by SSA/P (10-25%) and TSA (~1%), which concur the findings in our study (18,22-25).

The true prevalence of SSA/P might be under-reported, likely due to its subtle presentation and under-detected by means of colonoscopy (26). Other contributing factors might be due to difficulty in

Table II : Association between SSA/P and non SSA/P with demographic parameters and colonoscopic findings.

		SSA/P	Non SSA/P	
		n (%)		p value
Demographic parameters				
Gender				
	Male	21(15.6%)	114(84.4%)	0.596
	Female	8(12.7%)	55 (87.3%)	
Age				
	≥65 years old	17(16.7%)	85(83.3%)	0.429
	<65 years old	12(12.5%)	84(87.5%)	
Race				
	Chinese	17(15.5%)	93(84.5%)	0.840
	Others	12(13.6%)	76(86.4%)	
Colonoscopic findings				
Location of polyp				
Right side of colon		16(25.8%)	46(74.2%)	0.004*
Left side of colon		13(9.6%)	123 (90.4%)	
Size of polyp				
	≥10mm	9(40.9%)	13(59.1%)	0.013*
	<10mm	2(7.7%)	24(92.3%)	
	Missing data	18(12%)	132(88%)	

*Statistically significant (p<0.05)

histopathological evaluation, especially when the biopsy specimen is too superficial or tangentially cut (27,28). These are the most common findings that were encountered when reviewing the slides.

It is well-known that SSA/P could be under-diagnosed as HP (27,28). It is important to differentiate the histological features of SSA/P and HP, due to the risk of SSA/P to turn into CRC via a serrated pathway. Moreover, the management of both types of polyps is also different.

Multiple studies have shown that number of cases of SSA/P are underdiagnosed as HP, which concur with this study. In one study, one third of HP which are >5mm in size were reclassified into SSA/P (12). A study by Dada et al. (2013) (28) has shown that 42% of HP cases were reclassified to SSA/P. Another study concluded that the possibility for reclassification of HP to SSA/P is higher if HP is located in right colon, and is larger in size (>5mm in size) (29).

As in other studies, we noted that most of the polyps were superficial and tangentially cut, which contributed to improper histological interpretation. This problem was also encountered by other studies and deeper tissue sectioning was suggested for a better histological assessment and diagnosis (27,28). Another study has suggested on Ki67 immunohistochemistry to differentiate between SSA/P and HP; where in HP, the cells stained with Ki67 are mostly seen at the lower part of the colonic tubules. Meanwhile, for SSA/P, the Ki67 stained cells were seen throughout the tubules.

In this single center study, the incidence of SSA/P was more common in males, and there was no significant association between gender and SSA/P. Females were commonly reported to have SSA/P in some studies and with significant association (24,28,29). It is worth pointing out that the difference found in this study compared to previous studies might be due to the major population diagnosed with SCP was male (68.2%), which was, twice the number of the female population (31.8%).

In this study, the patients diagnosed with SSA/P were more common at the age of 65 or above, which concurred with several related studies. A few studies have shown that aging will increase the risk of DNA methylation which is one of the molecular features of SSA/P (30,31). However, the present study showed no significant association between SSA/P and age, which differed from some studies (24). More multicentered studies need to be conducted in the context of Malaysia to support this finding.

SSA/P appeared to be more common in the Chinese population compared to Malay and Indian. This is likely due to the study population being mostly Chinese (55.6%), followed by Malay (30.3%) and Indian (13.6%).

SSA/P was also noted in the right colon with a size of 10mm or more, and a significant association of those features with SSA/P was also revealed in multiple studies (6,9,32). In the present study, most data on the size of SSA/P from colonoscopy was unavailable. For cases with missing data, the size of polyps was measured during sampling in the laboratory. In some cases, the actual size could not be properly measured as the samples were received in multiple pieces or were not intact. Nevertheless, these significant associations in the present study came from one center population, and might not reflect the entire Malaysian population.

CONCLUSION

According to the results obtained in this study, there was some percentage of underdiagnosed cases of SSA/P amongst HP. This is likely due to their resemblance in microscopic features, where SSA/P mimics HP, and vice versa. The study findings also demonstrated that SSA/P was more common in the right colon, with a size of 10mm or more, and significantly associated. These findings may consider adjunctive features that may favour the diagnosis of SSA/P for ambiguous cases or in poorly oriented histological sections especially when

the polyps have serrated histological features. It is important to recognize different types of serrated polyps, especially SSA/P and TSA, as both are premalignant polyps and have a higher risk to turn into CRC.

A multicenter study involving a larger population is recommended to be conducted in Malaysia for more valid findings. A larger-scale study may also contribute to the prevalence of SSA/P, and may educate on the proper diagnosis of SCP.

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