Journal of Biosciences and Medicines, 2024, 12, 91-98
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Superficial Serrated Adenoma (SuSA): A New Subtype of Serrated Lesions

Rui Chen[1,2,3], Qing Zhang[1,2,3*]

[1]Department of Gastroenterology, The First Affiliated Hospital of Yangtze University, Jingzhou, China
[2]Digestive Disease Research Institution of Yangtze University, Jingzhou, China
[3]Clinical Medical College, Yangtze University, Jingzhou, China
Email: *835521152@qq.com

How to cite this paper: Chen, R. and Zhang, Q. (2024) Superficial Serrated Adenoma (SuSA): A New Subtype of Serrated Lesions. *Journal of Biosciences and Medicines*, **12**, 91-98.
https://doi.org/10.4236/jbm.2024.125008

Received: March 18, 2024
Accepted: May 13, 2024
Published: May 16, 2024

Abstract

Superficial serrated adenoma (SuSA) is a new subtype of serrated lesions proposed in recent years, most of which are located in the sigmoid colon or rectum, with typical mixed adenoma and serrated pathological features, and its molecular features are high frequency of KRAS mutation and RSPO fusion or overexpression. At present, it is believed that SuSA has two subtypes: traditional serrated adenoma (TSA)-associated SuSA and isolated SuSA. Solitary SuSA showed faded pedicle-free protuberant lesions under endoscope and lobulated, pp (pit pattern) classification was type II and type IIIH, TSA-associated SuSA showed double-layer eminence, SuSA part showed white flat eminence, pp classification showed type II and IIIH, TSA part showed red tone high eminence, pp was IVH type. SuSA can develop into colorectal cancer through the evolution of TSA, and it can also directly develop into MSS colorectal cancer. In view of the superficial understanding of SuSA and the lack of a complete description of SuSA, this paper review the research progress of SuSA at home and abroad from the origin, endoscope features, histopathological features, molecular biology, differential diagnosis and treatment of SuSA, in order to better promote the understanding and clinical diagnosis of lesions.

Keywords

Colorectal Cancer, Serrated Lesion, Superficial Serrated Adenoma, Colonoscopy

1. Introduction

Colorectal cancer (colorectal cancer, CRC) is one of the most common malig-

nant tumors in the world, ranking the third in the incidence of all cancers, the second in mortality, and the first in all cancers of the digestive system [1]. In recent years, with the improvement of people's health awareness and the increasing popularity of colonoscopy, digestive endoscopy doctors pay more and more attention to the diagnosis and treatment of early CRC. The premonitory signs of colorectal cancer include two pathways: conventional adenomas and serrated lesions. The classical approach of "adenoma-adenocarcinoma" put forward in the 1970s [2]. It is generally believed that adenomatous polyps are precancerous lesions of CRC. Although traditional adenoma is the main precursor of CRC carcinogenesis, another pathway, serrated lesion pathway, has been paid more and more attention in recent years. According to the literature, up to about 30% of colorectal cancer is thought to be caused by serrated lesions [3].

Colorectal serrated lesions are a group of heterogeneous lesions different from common polyps/adenomas. Their histological features are serrated structures in the colonic recess, which is the result of decreased apoptosis and increased senescence of epithelial cells in the recess [4]. According to the latest classification of digestive tumors in the 5th edition of the World Health Organization, serrated lesions include hyperplastic polyps (HP), sessile serrated lesion (SSL), sessile serrated lesion with dysplasia (SSL-D), traditional serrated adenomas (TSA) and serrated adenoma-unclassified [5]. At present, it is not clear which lesion type SuSA belongs to, but as a new subtype of serrated lesions, a case of adenocarcinoma originating from SuSA has been reported in the literature, indicating that SuSA has the nature of precancerous lesions [6]. In this paper, the research progress of SuSA at home and abroad is summarized as follows.

2. The Origin of SuSA

Superficial serrated adenoma (SuSA) is a new subtype of serrated lesion proposed by Hashimoto *et al.* in 2018. Most SuSA are located in the sigmoid colon or rectum of the left colon, showing typical mixed adenoma and serrated features, including straight adenoma glands, serrated only in the superficial part [6] [7]. According to related literature reports, SuSA has two subtypes: TSA-associated SuSA and isolated SuSA [8]. TSA-associated SuSA is easily detected when associated with TSA, so when we find it, it can be removed by us together with TSA [8]. On the contrary, if it is an isolated SuSA, the endoscopic manifestation is usually very small and is often indistinguishable from hyperplastic polyps, which may lead to some confusion [8] and mistake it for HP, resulting in recognition and ignorance. Therefore, it is necessary to understand the common endoscopic features of SuSA.

3. Endoscopic Features

The shape of SuSA shown by endoscopy is diverse, depending on the size of the lesion itself. The study of Mizuguchi *et al.* [9] shows that most SuSA are white in color, with clear boundaries, and lobulated structures are also common, espe-

cially in large lesions.

According to the size of endoscopic SuSA, it can be divided into three groups: diminutive (1 - 5 mm), small (6 - 9 mm), large (≥10 mm) [9].

Diminutive (1 - 5 mm): Endoscopic appearance is mostly round, often accompanied by slight eminence, indicating smooth, clear but irregular boundary; under magnifying pigment endoscope, the vascular morphology is not clear, and the JNET classification is type 1.

Small (6 - 9 mm): Endoscopy often showed faded tone, slight uplift without pedicle, uneven surface and lobulated structure; irregular surface structure could be seen under indigo staining, but the boundary was clear, and the blood vessels were not obvious under magnifying pigment endoscope, and the JNET classification was type 1.

Large (≥10 mm): The larger lesions showed flat eminence with lobulated structure (different iated from TA and SSL). Lengthening and branching could be seen on part of the surface, and the boundary was clear but irregular. The blood vessels seen under magnifying pigment endoscope are not obvious or very few can be shown as reticular vessels [9]. The irregular lobulated surface structure can be seen after indigo staining, and the pitting type II or IIIH can be observed by magnifying endoscopy, indicating that SuSA has a consistent serrated surface microstructure [9]. However, in all the SuSA we found, endoscopy did not show mucus cap coverage [9].

4. Histopathological Features

Histopathologically, SuSA mainly showed typical mixed adenoma and serrated features [8]. It mainly includes the straight adenomatous gland and the superficial part of the serrated structure, the middle and lower layer of non-serrated glands, the cells are columnar, the bottom of the cell nuclear base is slender and uniform [7], showing a typical "second floor". Under the microscope, a clear boundary can be seen in the pathological section, there is a sudden transition between the neoplastic gland and the normal mucosa around the lesion, and the superficial layer of the lesion can be seen with serrated process + middle-deep adenomatoid glandular hyperplasia. Immunohistochemistry showed that CK20 was expressed in the upper layer of SuSA, similar to that in normal mucosa, Ki 67 and MYC were expressed in the middle and lower layer of SuSA, and SuSA showed not only membranous β-catenin expression, but also moderate nuclear β-catenin expression [7].

5. Molecular Biological Characteristics

Up to now, simultaneous KRAS mutation and RSPO fusion/overexpression are often found in most SuSA [9]. RSPO fusion and overexpression that lead to activation of WNT signal transduction are common and specific for SuSA and TSA [10]. Another remarkable feature of SuSA is its frequent coexistence with TSA. Previous studies have shown that there are the same KRAS mutations and

RSPO fusion or overexpression in the related components of SuSA and TSA, which confirmed their tissue relationship, but the mere existence of KRAS mutation and RSPO fusion or overexpression is not enough to promote the development of SuSA into TSA, and other unknown factors are needed [7] [11]. SuSA is mostly sessile lesions, lacking the pedicled or subpedicled morphology and typical cytology, ectopic recess formation and fissure serrated characteristics of TSA, so it is difficult to determine the morphological relationship between isolated SuSA and TSA, and only about 30% of TSA have KRAS mutations and RSPO fusion or overexpression, indicating that not all TSA originate from SuSA, but part of them originate from SuSA [7] [8]. Compared with TSA, the lesion size of SuSA is smaller.

6. Differential Diagnosis

SuSA usually needs to be differentiated from SSL, SSLD, and TA in endoscopic morphology and histology, but tiny SuSA is more likely to be confused with proliferative polyps. Therefore, the main identification points of SuSA, HP, SSL and so on are mainly given here.

7. Under Endoscope

The most common site of SuSA is located in the sigmoid colon or rectum. The color is white and has a clear boundary. The lobulated structure is especially prominent in large lesions. The mucus cap is often invisible, and bright blue ridge (LBC) and white opaque substance (WOS) are often seen in white light and narrow band imaging (NBI). Under magnifying pigment endoscope, most of the openings of glandular duct showed II, II-L and III-H [7].

About 70% of HP is located in the left colon, usually <5 mm in diameter [12]. Under white light endoscope, HP is transparent or pale, usually similar to the surrounding mucosa, round or oval, and the shape is flat [13] [14]. Brown reticular capillaries could not be observed under magnifying pigment endoscope, and the opening of glandular duct was type II [15]. The most common site of SSL is located in the right colon. Endoscopic screening shows that mucus cap is an important "clue" to find SSL. LBC is often not visible under white light and NBI, while WOS is only sometimes visible. Pale, flat or sessile shape can be seen under white light endoscope, with the characteristics of cloud-like appearance, irregular surface, mucous cap and blurred edges [16]. The black spot sign was observed in NBI mode [17]. Under magnifying pigment endoscope, most of the openings of glandular duct were II-O and II.

8. Histologically

SuSA is mainly composed of vertical adenomatous glands. The transformation between superficial serrated glands in the outer layer and non-serrated glands in the middle and lower layers can be seen. The cells are columnar and the base of the nucleus is slender and uniform. The base of the recess is usually straight and

does not have the characteristics of SSL, but larger lesions have some dilated glands, and all lesions are not accompanied by other types of polyps, such as HP or SSL [7].

In the new WHO classification, HP is divided into microvesicular type (MVHP) and goblet cell-rich type (GCHP). MVHP is common in the right colon, and its zigzag structure is limited to the crypt. The cells in the crypt are composed of microbubble cells and goblet cells, of which MVHP is dominant, while GCHP is often located in the left colon, with few serrated structures and abundant goblet cells in the crypt [18].

According to the classification of WHO in 2019, SSL can be diagnosed with only one "characteristic" recess, that is, more than one developed horizontally along the mucosal muscle, bottom dilatation, zigzag changes reaching the bottom, asymmetric proliferation and so on [5]. Its remarkable feature is that the recess is twisted and usually expands toward the base, showing a boot-shaped, L-shaped or inverted T-shaped [15] [19], and the jagged change is most obvious at the base.

9. Therapy

At present, a case of adenocarcinoma originating from SuSA has been reported in the literature, which shows that SuSA has the nature of precancerous lesion [6], so endoscopic resection is recommended as soon as it is found. The common methods of endoscopic surgery are as follows:

Cold snare polypectomy(CSP) has high complete resection rate and low delayed bleeding rate. It is very suitable for serrated lesions of lt; 10 mm [20]. Some studies have confirmed that the complete resection rate of CSP is significantly better than that of cold forceps polypectomy in terms of the integrity of small polyps [21]. The principle of CSP is to ensure the removal of the normal edge of the surrounding 1/2 mm [20], which not only ensures the complete resection rate and low delayed bleeding, but also avoids the thermal injury caused by thermal resection of polyps (hot snare polypectomy, HSP).

Endoscopic mucosal resection (EMR) is the first choice for lesions ≥10 mm [22]. According to related studies, for serrated lesions ≥10 mm, EMR can not only ensure the safety of lesion resection, but also ensure a low recurrence rate [23].

For some lesions ≥20 mm, or TSA-related SuSA, we need to use endoscopic submucosal dissection (ESD) as a resection method. Of course, some studies have shown that piecewise EMR resection can be used to treat serrated lesions ≥20 mm, but it still has a significant recurrence rate [24], so it is generally not recommended as a treatment.

For some lesions that cannot be removed under endoscope, such as 50 mm, 60 mm or larger, there may be severe submucosal fibrosis, endoscopic treatment with perforation and a high risk of perioperative bleeding; or some lesions with submucosal invasive cancer, endoscopic treatment will increase the risk of incomplete resection, for these lesions can be treated by surgery.

10. Summary and Prospect

The morbidity and mortality of CRC are on the rise in China, and the malignant transformation pathways of different pathological types of colorectal polyps are different. At present, we know that about 30% of colorectal cancer originates from "serrated lesion-cancer pathway". Although we have a certain understanding of the morphology, pathological tissue and molecular characteristics of colorectal serrated lesions, however, the pathogenesis of cancerization through the serrated pathway still needs further study. In the understanding of SuSA, it is feasible to diagnose isolated SuSA with large correlation between SuSA and TSA under endoscope. In recent years, it has also been found that some subtypes of HP can develop into some precursors of colorectal cancer through zigzag pathways [25]. For example, MVHP may be the precursor of sessile serrated adenoma, and GCHP may be the precursor of TSA [26] [27], but it still needs to be confirmed. At present, a case of adenocarcinoma originating from SuSA has been reported in the literature, and it has also been found that some subtypes of HP can also develop into precursors of colorectal cancer, so improving the understanding and differentiation of SuSA and HP is helpful to better understand the occurrence and development of colorectal tumors.

In the future, it is still challenging to identify isolated tiny SuSA and HP, because their morphological characteristics are similar and we need to constantly accumulate and explore. As for SuSA, a new subtype of serrated lesions, how should we understand whether it is only a precursor of TSA or may be divided into a new subtype independently, we need to further understand the differences in clinicopathology and molecular characteristics. The identification of new pathways in colorectal cancer could give researchers and clinicians the opportunity to address this challenge by optimizing screening to further prevent the onset and progression of colorectal cancer. In the future, more clinical case analysis is needed to clarify the characteristics of this novel serrated lesion and epigenetic characteristics, so as to further improve the development of colorectal cancer serrated pathway, which will help to stratify the risk of patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Muto, T., Bussey, H.J. and Morson, B.C. (1975) The Evolution of Cancer of the Colon and Rectum. *Cancer*, **36**, 2251-2270. https://doi.org/10.1002/cncr.2820360944

[3] Pai, R.K., M€Akinen, M.J. and Rosty, C. (2019) Colorectal Serrated Lesions and Polyps. In: WHO Classification of Tumours Editorial Board, Ed., *Disgetive System*

Tumours, International Agency for Research on Cancer (IARC), Lyon, 163-170.

[4] Geramizadeh, B. and Robertson, S. (2017) Serrated Polyps of Colon and Rectum: A Clinicopathologic Review. *Journal of Gastrointestinal Cancer*, **48**, 291-298. https://doi.org/10.1007/s12029-017-9977-y

[5] Nagtegaal, I.D., Odze, R.D., Klimstra, D., *et al.* (2020) The 2019 WHO Classification of Tumours of the Digestive System. *Histopathology*, **76**, 182-188. https://doi.org/10.1111/his.13975

[6] Mizuguchi, Y., Sakamoto, T., Hashimoto, T., *et al.* (2019) Identification of a Novel PRR15L-RSPO2 Fusion Transcript in a Sigmoid Colon Cancer Derived from Surfically Serrated Adenoma. *Virchows Archiv*, **475**, 659-663. https://doi.org/10.1007/s00428-019-02604-x

[7] Hashimoto, T., Tanaka, Y., Ogawa, R., *et al.* (2018) Superficially Serrated Adenoma: A Proposal for a Novel Subtype of Colorectal Serrated Lesion. *Modern Pathology*, **31**, 1588-1598. https://doi.org/10.1038/s41379-018-0069-8

[8] Togashi, K. (2022) Superficially Serrated Adenoma: Novel Precursor in the Serrated Pathway. *Digestive Endoscopy*, **34**, 77-78. https://doi.org/10.1111/den.14074

[9] Mizuguchi, Y., Tanaka, Y., Cho, H., *et al.* (2022) Endoscopic Features of Isolated and Traditional Serrated Adenoma-Associated Superficially Serrated Adenomas of the Colorectum. *Digestive Endoscopy*, **34**, 153-162. https://doi.org/10.1111/den.13992

[10] Sekine, S., Yamashita, S., Tanabe, T., *et al.* (2016) Frequent PTPRKRSPO3 Fusions and RNF Mutations in Colorectal Traditional Serrated Adenoma. *The Journal of Pathology*, **239**, 133-138. https://doi.org/10.1002/path.4709

[11] McCarthy, A.J., Serra, S. and Chetty, R. (2019) Traditional Serrated Adenoma: An Overview of Pathology and Emphasis on Molecular Pathogenesis. *BMJ Open Gastroenterology*, **6**, e000317. https://doi.org/10.1136/bmjgast-2019-000317

[12] Crockett, S.D. and Nagtegaal, I.D. (2019) Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. *Gastroenterology*, **157**, 949-966.E4. https://doi.org/10.1053/j.gastro.2019.06.041

[13] Vleugels, J.L., IJspeert, J.E. and Dekker, E. (2015) Serrated Lesions of the Colon and Rectum: The Role of Advanced Endoscopic Imaging. *Best Practice & Research Clinical Gastroenterology*, **29**, 675-686. https://doi.org/10.1016/j.bpg.2015.05.009

[14] Kahi, C.J., Vemulapalli, K.C., Snover, D.C., *et al.* (2015) Findings in the Distal Colorectum Are Not Associated with Proximal Advanced Serrated Lesions. *Clinical Gastroenterology and Hepatology*, **13**, 345-351. https://doi.org/10.1016/j.cgh.2014.07.044

[15] Cassese, G., Amendola, A., Maione, F., *et al.* (2019) Serrated Lesions of the Colon Rectum: A Focus on New Diagnostic Tools and Current Management. *Gastroenterology Research and Practice*, **2019**, Article ID: 9179718. https://doi.org/10.1155/2019/9179718

[16] Hazewinkel, Y., López Cerón, M., East, J.E., *et al.* (2013) Endoscopic Features of Sessile Serrated Adenomas: Validation by International Experts Using High Resolution White Light Endoscopy and Narrow Band Imaging. *Gastrointestinal Endoscopy*, **77**, 916-924. https://doi.org/10.1016/j.gie.2012.12.018

[17] Saito, S., Tajiri, H. and Ikegami, M. (2015) Serrated Polyps of the Colon and Rectum: Endoscopic Features Including Image Enhanced Endoscopy. *World Journal of Gastrointestinal Endoscopy*, **7**, 860-871. https://doi.org/10.4253/wjge.v7.i9.860

[18] Pai, R.K., Bettington, M., Srivastava, A., *et al.* (2019) An Update on the Morphology and Molecular Pathology of Serrated Colorectal Polyps and Associated Carcinomas.

Modern Pathology, **32**, 1390-1415. https://doi.org/10.1038/s41379-019-0280-2

[19] Ma, M.X. and Bourke, M.J. (2017) Sessile Serrated Adenomas: How to Detect, Characterize and Resect. *Gut and Liver*, **11**, 747-760. https://doi.org/10.5009/gnl16523

[20] Kim, J.S., Lee, B.I., Choi, H., *et al.* (2015) Cold Snare Polypectomy versus Cold Forceps Polypectomy for Diminutive and Small Colorectal Polyps: A Randomized Controlled Trial. *Gastrointestinal Endoscopy*, **81**, 741-747. https://doi.org/10.1016/j.gie.2014.11.048

[21] Raad, D., Tripathi, P., Cooper, G., *et al.* (2016) Role of the Cold Biopsy Technique in Diminutive and Small Colonic Polyp Removal: A Systematic Review and Meta Analysis. *Gastrointestinal Endoscopy*, **83**, 508-515. https://doi.org/10.1016/j.gie.2015.10.038

[22] Gupta, V. and East, J.E. (2020) Optimal Endoscopic Treatment and Surveillance of Serrated Polyps. *Gut and Liver*, **14**, 423-429. https://doi.org/10.5009/gnl19202

[23] Rao, A.K., Soetikno, R., Raju, G.S., *et al.* (2016) Large Sessile Serrated Polyps Can Be Safely and Effectively Removed by Endoscopic Mucosal Resection. *Clinical Gastroenterology and Hepatology*, **14**, 568-574. https://doi.org/10.1016/j.cgh.2015.10.013

[24] Pellise, M., Burgess, N.G., Tutticci, N., *et al.* (2017) Endoscopic Mucosal Resection for Large Serrated Lesions in Comparison with Adenomas: A Prospective Multicentre Study of 2000 Lesions. *Gut*, **66**, 644-653. https://doi.org/10.1136/gutjnl-2015-310249

[25] Bettington, M., Walker, N., Clouston, A., *et al.* (2013) The Serrated Pathway to Colorectal Carcinoma: Current Concepts and Challenges. *Histopathology*, **62**, 367-386. https://doi.org/10.1111/his.12055

[26] Rashtak, S., Rego, R., Sweetser, S.R., *et al.* (2017) Sessile Serrated Polyps and Colon Cancer Prevention. *Cancer Prevention Research* (*Phila*), **10**, 270-278. https://doi.org/10.1158/1940-6207.CAPR-16-0264

[27] Okamoto, K., Kitamura, S., Kimura, T., *et al.* (2017) Clinicopathological Characteristics of Serrated Polyps as Precursors to Colorectal Cancer: Current Status and Management. *Journal of Gastroenterology and Hepatology*, **32**, 358-367. https://doi.org/10.1111/jgh.13482