Digestive and Liver Disease 47 (2015) 95–102

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Sessile serrated adenoma: From identification to resection

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ARTICLE INFO

Article history:
Received 26 August 2014
Accepted 13 September 2014
Available online 25 October 2014

Keywords:
Colonoscopy
Colorectal cancer
Histology
Molecular pathology
Serrated adenoma

ABSTRACT

Until the past two decades, almost all colorectal polyps were divided into two main groups: hyperplastic polyps and adenomas. Sessile serrated adenomas presented endoscopic, pathological and molecular profiles distinct from others polyps. Previously under-diagnosed, physicians now identified sessile serrated adenomas. The serrated neoplastic pathway is accounting for up to one-third of all sporadic colorectal cancers and sessile serrated adenomas have been identified as the main precursor lesions in serrated carcinogenesis. By analogy with the adenoma–adenocarcinoma sequence, the sessile serrated adenomas–adenocarcinoma sequence, has been identified. The development of endoscopic resection techniques permits the consideration of a non-surgical approach as the first option regardless of the size of the lesion. Sessile serrated adenoma warrants the watchfulness of physicians and requires an optimal quality of the colonoscopy procedure, a thorough evaluation of the lesion, an adequate endoscopic resection and follow-up colonoscopies in accordance with sessile serrated adenomas guidelines. We herein present a review on sessile serrated adenomas focusing on their pathological specificities, epidemiology, treatment modalities and follow-up.

1. Introduction

Until the past two decades, almost all colorectal polyps were divided into two main groups: hyperplastic polyps and adenomas. Hyperplastic polyps constitute a very common type in western population with an estimated prevalence of 20%, accounting for one-third of all resected polyps. Hyperplastic polyps are characterized by their "saw-tooth" appearance on microscopy analysis from the folding in of the crypt epithelium. Colorectal adenomas have been identified as a pre-neoplastic lesion following the adenoma – colorectal cancer sequence [1,2]. This finding justified colorectal cancer screening programmes leading to the resection of all adenomas in order to reduce colorectal cancer incidence [3].

In 1990, Longacre and Fenoglio-Preiser noticed that some "serrated" polyps shared features with both conventional adenomas and hyperplastic polyps, and thereby coined these polyps "traditional serrated adenomas" [4]. In 1996, Torlakovic et al. identified another subset of serrated lesions within "hyperplastic polyposis", displaying an abnormal architecture without cytological dysplasia and defined them as "sessile serrated adenomas" (SSAs), which are now considered as precursors of microsatellite unstable colorectal carcinomas [5,6]. The prevalence of SSAs has been underestimated for years, ranging from 0.1% to 14.7% of all colorectal polyps [7,8]. The definition of this new entity requires particular attention and SSAs should be differentiated from conventional colorectal adenomas. We herein present a review on SSAs focusing on their pathological specificities, epidemiology, treatment and follow-up modalities.

2. Histological and bio-molecular features

2.1. Histological architecture

Serrated polyps are divided into three main categories using the WHO classification of tumours of the digestive system [9]: typical hyperplastic polyps, SSAs and traditional serrated adenomas. In this classification, SSA and "sessile serrated polyp" are synonymous terms and both are acceptable diagnostic terms. Histological diagnostic criteria of serrated lesions are presented in Table 1. As all serrated lesions, SSAs are characterized by their jagged appearance

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http://dx.doi.org/10.1016/j.dld.2014.09.006
1590-8658/

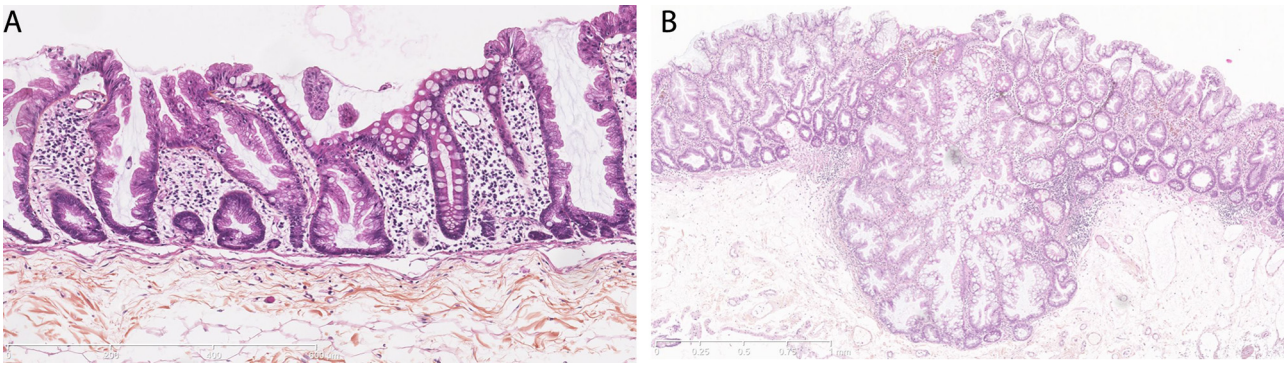

Fig. 1. Histological features of sessile serrated adenomas on microscopy analysis.

on microscopy analysis. They display a larger size than hyperplastic polyps and mostly occur in the proximal colon. The diagnosis is based mainly on architectural features with a disorganized and distorted crypt growth pattern. Major differences between hyperplastic polyps and SSAs concern the basal portion of the polyp. Indeed, the serrations affect the entire length of the crypt, bottom included for sessile serrated adenoma/polyp (Fig. 1A). Crypt bases appear dilated or irregularly branched, with horizontal extension forming an "L" or inverted "T" shape, unlike other serrated lesions that do not display an abnormal architecture in that area. These findings demonstrate that hyperplastic polyps and sessile serrated adenoma/polyps are difficult to distinguish from one another in case of superficial biopsies or electrocautery artefacts resulting from endoscopic resection [10].

SSAs crypts tend to arrange themselves parallel to the muscularis mucosa and sometimes even beneath this layer thus achieving herniation through it (Fig. 1B). They are lined with columnar secreting clarified cells, and generally less eosinophil cells in traditional serrated adenoma than in adenoma. Mature goblet and mucinous cells are found within the base of the crypts and trigger excessive mucous production which often results in the presence of mucin in the lumen of dilated crypts. Such characteristics are not observed in hyperplastic polyps where the lowest third of the crypts remain narrow and lined with proliferative cells.

Table 1
Types of serrated lesions and their histological features.

Types of serrated lesions	Histological features
Hyperplastic polyps (goblet cell, microvesicular and mucinous poor-hyperplastic polyps)	• Local mucosal thickening • Serration more pronounced in the upper half of the crypts • Linear and straight crypts without distortion • Epithelium lined with different cells (microvesicular mucinous, goblet or undifferentiated) depending on variants of hyperplastic polyps
Traditional serrated adenoma	• Eosinophilic cytoplasm and elongated nuclei • Crypt budding • Distorted villous or tubulo-villous architecture
Sessile serrated adenoma	• Dilated and/or branched crypts • Saw-tooth appearance involves the entire length of the crypt, including crypt base • Horizontal extension of crypt bases • Herniation of crypts through the muscularis mucosa • Cytological dysplasia is mostly missing

SSAs may harbour cytoplasmic and nuclear atypia with features similar to both low-grade and high-grade dysplasia in conventional adenomas, which is considered as an indicator of a higher risk of rapid progression to colorectal cancer [11]. SSAs have been under-diagnosed by pathologists and often wrongly considered as hyperplastic polyps as illustrated by a recent study from Gill et al. in which three pathologists blinded to the original diagnosis re-examined the slides of all right sided polyps first labelled as hyperplastic polyps and re-classified 30–64% of them as SSAs [12].

According to the American Gastroenterology Association, only one crypt showing the characteristic features is sufficient for the diagnosis of SSA while in the WHO classification at least three crypts (or two adjacent crypts) should be present for the diagnosis [13]. This discrepancy induces a significant impact on SSA prevalence [7]. With a strict application of the diagnostic criteria outlined in the last edition (2010) of the WHO classification, Bettington et al. identified that SSAs represented 12.1% of all polyps [7]. The incidence raised to 14.7% applying criteria of the American Gastroenterology Association.

The third category of serrated polyp corresponds to the traditional serrated adenoma. It usually shows a protuberant exophytic configuration, complex villous growth architecture and an abundance of columnar cells with eosinophilic cytoplasms. A characteristic pattern of budding of proliferative crypts situated perpendicular to the long axis of villous structures is frequently observed. Both conventional adenoma-like dysplasia and serrated dysplasia can be encountered in traditional serrated adenomas. The overall prevalence of traditional serrated adenoma and SSAs was 0.6% and 2.3%, respectively [14].

Due to terminology problems and histologic overlap among the features of these different serrated lesions, pathologists encounter some difficulties in classifying some lesions. However, few studies have evaluated the reproducibility of light microscopic diagnosis of serrated polyps among pathologists and reported a moderate to good agreement for polyp classification ($\kappa = 0.56–0.63$) [15,16].

2.2. Serrated neoplastic pathway

In contrast with the adenoma – adenocarcinoma sequence occurring through chromosomal instability, responsible for progressive accumulation of mutations in oncogenes and tumour-suppressor genes, the serrated neoplastic pathway is characterized by aberrant methylation in promoter regions of specific genes. This epigenetic mechanism is based on hyper-methylation within sequences of pairs of cytosine and guanine nucleotides, called CpG islands, found in promoter regions of genes. These alterations result in the "CpG islands methylator phenotype" (CIMP) at either low or high degree which reduces gene expression without altering the DNA sequence. Hyper-methylation may occur in DNA mismatch repair gene (MMR) hMLH-1 associated with the development of