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Traditional serrated adenoma: an update

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Summary Although recognized 25 years ago, the traditional serrated adenoma (TSA) remains an ongoing source of diagnostic and biologic debate. Recent research has greatly improved our understanding of the morphological and molecular aspects of these polyps. In particular, the recognition of ectopic crypt foci (ECFs) in combination with typical cytology and slitlike serrations improves diagnostic reproducibility. Awareness that many TSAs, particularly *BRAF*-mutated TSAs, arise in precursor microvesicular hyperplastic polyps and sessile serrated adenomas can aid in making this diagnosis and should not be confused with a sessile serrated adenoma with dysplasia. At a molecular level, TSAs can be divided into 2 groups based on their *BRAF* or *KRAS* mutation status. The development of overt cytologic dysplasia is accompanied by *TP53* mutation, Wnt pathway activation, and, in some cases, silencing of *CDKN2A*. Importantly, however, mismatch repair enzyme function is retained. Thus, the TSA is an important precursor of aggressive molecular subtypes of colorectal carcinoma.

1. Introduction and history

In 1984, Urbanski et al [1] described an adenocarcinoma arising within an unusual colonic polyp. This polyp was characterized by a "mixed morphology" of hyperplastic and adenomatous areas. Although not using the term *serrated polyp*, this perhaps is the first description of a polyp with a serrated luminal profile and harboring conventional adenomatous dysplasia [1]. The authors of this article described the serrated areas as "papillary infolding, with cells exhibiting strong cytoplasmic eosinophilia, goblet cell dystrophy, and varying degrees of dysplasia" [1].

The traditional serrated adenoma (TSA) was first reported by Longacre and Fenoglio-Preiser [2] in 1990 under the more generic label of serrated adenoma. They described a polyp with admixed features of hyperplastic polyp and conventional adenoma. Many had a distinctive cytology, characterized by abundant eosinophilic cytoplasm and centrally placed, penicillate nuclei. This polyp was subsequently confused with subsets of sessile serrated adenomas (SSAs), sessile serrated adenomas with dysplasia (SSAD), and tubulovillous adenomas (TVAs) with architectural serration. Much of the confusion was removed in 2003 when Torlakovic et al [3] published their seminal article describing the histologic features of the SSA. At the same time, they designated the original "serrated adenoma" as the TSA to better separate it from the newly described SSA. Subsequently, they have addressed key diagnostic features of the TSA, with a particular focus on the importance of ectopic crypt formations or foci (ECFs) [4]. The fourth edition of the *World Health Organization Classification of Tumours of the Digestive Tract* emphasizes protuberant and villiform growth and ECFs in the diagnosis, reflecting the findings of these important articles [5].

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Our understanding of the molecular biology of TSAs has also continued to evolve. MAP kinase pathway activation is established as a critical early (probably initiating) event and occurs by either activating *BRAF* or *KRAS* mutation [6-9]. The CpG island methylator phenotype (CIMP) then develops in a subset of TSAs as a direct result of these initial mutations [10,11]. Interrogation of the histologic and molecular events that occur as these polyps progress toward carcinoma has been more limited, but a few recent articles have enhanced our understanding of this process [6,7,12].

In this review, we aim to highlight advances in the clinicopathological and molecular understanding of the TSA that have occurred since the publication of the fourth edition of the *World Health Organization Classification of Tumours of the Gastrointestinal Tract* [5] and to frame this in a manner helpful to the practicing pathologist. In particular, we will address the issues of diagnostic features, precursor polyps, dysplasia in the context of a TSA, and the molecular subtypes of carcinoma expected to arise from these lesions.

2. Clinicopathological and endoscopic features

Traditional serrated adenomas are rare polyps, comprising 0.56% to 1.9% of all colorectal polyps [2,13-16]. The mean size at diagnosis ranges from 9 to 14 mm, there is no obvious sex predilection, and they are mostly distal and protuberant [6-9,14,16]. The mean age at diagnosis tends to be in the sixth or seventh decade. The endoscopic appearances of the TSA have not been extensively investigated, but a pine cone–like appearance has been described [17]. Using magnification chromoendoscopy, they have a fernlike or stellate pit pattern [18]. Macroscopically, TSAs can be either sessile or protuberant [18]. Proximal cases are more likely to be sessile than distal lesions [6].

Because of their rarity, current surveillance guidelines for TSAs are based on limited evidence. At present, the US Multi-Society Task Force on Colorectal Cancer recommends a 3-year surveillance interval after a diagnosis of a TSA [19].

3. Diagnostic criteria and guidelines – recent advances and distinction from other polyps

There have been considerable recent advances in the histologic diagnosis of the TSA (see Fig. 1 for a morphological comparison of serrated polyps and the diagnostic features of TSA). In 2008, ECFs gained attention as a feature helpful to identify TSAs and to distinguish them from SSAs [4]. Ectopic crypt foci are recognized as epithelial buds with their bases not anchored to or seated on the muscularis mucosae and are found along the sides of the villous projections of the polyp (Fig. 1G). Some have regarded that these ECFs are the proliferation zone of TSAs, but the Ki-67 proliferation in these foci is not always high. More recently, it has been recognized that a subset of TVAs also harbors ECFs [20,21]. In addition, some TSAs, in particular, small polyps, do not show ECFs [6,8]. Several recent publications have reemphasized the striking similarity between the TSA and the normal small bowel epithelium as a critical component of the diagnosis [6,20-22]. In particular, the characteristic cytologic appearance of the TSA and the presence of a distinctive form of serration are very useful clues to making the diagnosis. The typical cell of the TSA is one with plentiful, intensely eosinophilic cytoplasm and centrally placed, palisaded, penicillate nuclei. These cells are so characteristic of the TSA that, outside the setting of the very rare goblet cell–rich variant, it is very difficult to justify this diagnosis if they are not the predominant component. Conversely, although small patches of cells with these features can be seen frequently in other polyp types, it is very unusual to see a polyp comprised predominantly of these cells that does not qualify to be diagnosed as a TSA. In tight association with this cytology are the characteristic epithelial serrations. These have been described variously as "slitlike" or "table top" but essentially describe the same feature [6,21]. Although the classic TSA cytology can be seen on its own, slitlike serrations essentially always accompany the eosinophilic cells. When seen together, the diagnosis of TSA must always be considered, regardless of the presence or absence of ECFs. That being said, most TSAs greater than 10 mm in diameter will have all 3 features [6]. Although protuberant growth and distal location have been emphasized in the past, it is now becoming clear that sessile and proximal TSAs are relatively common. These TSAs are mostly *BRAF* mutated and have frequent origin in a precursor polyp, in particular, microvesicular hyperplastic polyps (MVHPs) and SSAs [6,8].

This concept of TSAs arising in MVHPs/SSAs is not new but remains surprisingly controversial [4,23,24]. In our opinion, this finding has now been so well documented by numerous groups that it should no longer be an issue of debate. In fact, 30% to 50% of TSAs appears to arise in 1 of these precursors [6,8,9,22]. The relative proportions arising in MVHPs versus SSAs are somewhat variable and likely reflect differences in diagnostic criteria. Groups that use the single-crypt criteria for the diagnosis of a SSA are likely to have higher proportions of SSA than other groups [13,25]. More important in this context is recognition of the TSA component (as this will dictate the surveillance interval) and separating this process from dysplasia arising in an SSA. This issue will be discussed further in a subsequent section.

The final morphological point of discussion relates to the controversial concept of dysplasia in the TSA. Many (probably most) pathologists consider the TSA to be inherently dysplastic and routinely report low-grade dysplasia in TSAs mainly based on elongated, penicillate nuclei. We propose an alternate view, using the same schema as is accepted for the SSA and SSAD. In our view, although the ordinary TSA is undoubtedly neoplastic, it does not have inherent cytologic dysplasia. The eosinophilic cells of an ordinary TSA are not overtly atypical, do not show mitoses,