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Letter to the Editors

## Dysplasia in traditional serrated adenoma

*Dear Sir,*

I write after reading the excellent review by Dr. Snover in a recent issue of *Annals of Diagnostic Pathology* [1].

In particular, I would like to draw reference to traditional serrated adenoma (TSA), a well-recognized type of polyp within the serrated polyp rubric and considered *sui generis* based on characteristic morphology [2,3].

The molecular pathogenesis is complex but TSA show *KRAS*, *BRAF*, *RNF-43* mutations, *PTPRK-RSPO3* fusions and activation of the Wnt-signaling pathway [4-6]. However, how all these molecular events translate collectively into morphological findings is also complex and not straight forward.

The morphology of the majority of TSA is typified by tall eosinophilic cells with euchromatic, basally aligned, penicillate nuclei, a dearth of mitoses and a degree of uniformity throughout the polyp which Dr. Snover refers to as “enteric metaplasia” [1] (Fig. 1a). The resemblance to small bowel mucosa is striking. There are then cases that show the cytological features of adenomatous low-grade and/or high-grade dysplasia akin to the dysplasias seen in tubular/villous adenomas (Fig. 1b–d). Thus, there is a morphological distinction between the cytological features encountered in usual classic TSA (with enteric type cells) as opposed to those showing readily recognizable features of adenomatous dysplasia (low- or high-grade). Tsai and colleagues segregated TSA into those with so-called serrated dysplasia (*BRAF* mutated) and those with adenomatous dysplasia (*KRAS* mutated) [6]. Serrated dysplasia is defined by Snover as “mitotically active, moderately pleomorphic cells that are low columnar or cuboidal and have abundant eosinophilic cytoplasm” [1]. Low-grade serrated dysplasia in a TSA is illustrated in Fig. 1e.

High-grade serrated dysplasia is typified by oval to round nuclei, vesicular or hyperchromatic nuclei, thick nuclear membranes, prominent nucleoli, mitoses and pleomorphism (as demonstrated in Fig. 1f).

The difficulty arises in the nomenclature and codification of dysplasia in the typical TSA and, those with features of dysplasia (irrespective of whether serrated or adenomatous).

Hashimoto and colleagues, allude to the debate whether TSA are intrinsically dysplastic or not [6]. As mentioned above, the commonly seen TSA is made up of a uniform population of tall eosinophilic cells bearing elongated (penicillate) nuclei with finely dispersed chromatin, often delicate nuclear grooves, pinpoint nucleoli and desultory (if any) mitoses: enteric metaplasia. However, Hashimoto et al. contend that the cytological findings of usual TSA (enteric metaplastic cells) are **not** encountered in any other kind of polyp or even reactive conditions and, that the cytological features result from mutations in the Wnt pathway [6]. They conclude that “TSAs are inherently dysplastic” [6].

Since the morphology of TSA is so characteristic and not encountered in any other lesion, there is no need to open a polemic debate on whether they are *ab initio* dysplastic or not. However, it should be recognized then that this is a “special form of cytological appearance”, very reminiscent of small intestinal surface mucosa cells and encountered only in TSA. If this is considered the inherent baseline, cytology of TSA, then the advent of dysplasia (either serrated or adenomatous) should be regarded as evidence of progression.

For the purposes of simplicity and reproducibility, there is no reason at this juncture to believe that TSA with serrated dysplasia will behave differently to a TSA with the same grade of adenomatous dysplasia. Thus, dysplasia in a TSA is recognized by its deviation from the baseline cytology (enteric metaplasia) of the commonly encountered TSA.

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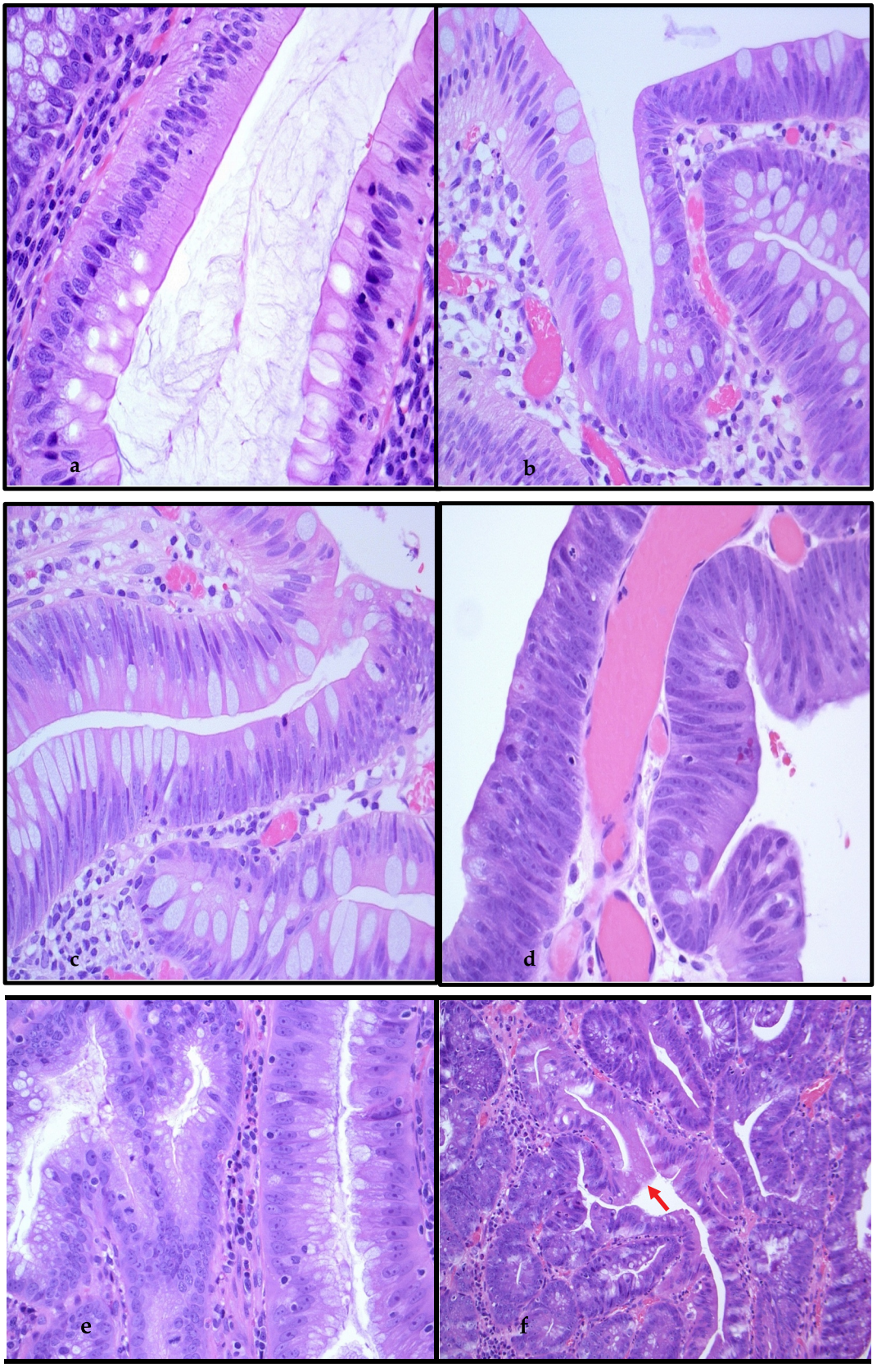


(caption on next page)

**Fig. 1.** a: The usual or classical TSA is recognized by intense cytoplasmic eosinophilia, a prominent luminal brush border, slit-like clefts and very distinct nuclear features. The nuclei are described as penicillate or elongated, have delicate, finely dispersed chromatin, often contain longitudinal grooves and have small nucleoli. The nuclei although pseudostratified are generally still basal in locale and show very occasional mitoses. This would be considered baseline cytology (dysplasia) for TSA that do not have superimposed low-grade serrated/adenomatous dysplasia. b–d: The image in panel 'b' illustrates the transition between baseline dysplasia (on the left) blending into obvious adenomatous dysplasia on the right. Under higher magnification, the early (c) and later (d) adenomatous dysplastic change from baseline cytological features, can be appreciated. The epithelium displays increasing nuclear stratification, nucleomegaly, larger nucleoli and mitoses. e: Low-grade serrated dysplasia is typified by rounder, more oval nuclei with prominent nucleoli, stratification and mitoses. Irrespective of whether serrated or adenomatous, these nuclear features are quite different from the baseline features illustrated in panel 'a'. f: High-grade serrated dysplasia is recognized by complexity of architecture (crowding of glands) together with cytological atypia: large hyperchromatic, pleomorphic nuclei, nuclei present at the luminal surface of the glands and brisk mitotic activity. Remnants of the more usual epithelium seen in TSA are apparent in the middle of the image (arrow).

A suggested practical approach to reporting TSA should be as follows:

1. The commonly encountered, caricature TSA with cytological uniformity (resemblance to small intestinal mucosa or enteric metaplasia), should be labelled ***"traditional serrated adenoma without serrated or adenomatous dysplasia"***.
2. Should morphologically recognizable dysplasia (either serrated or adenomatous; low-or high-grade) be present, then the report should read: ***"traditional serrated adenoma with low- or high-grade dysplasia"***. Perhaps the appellation *"advanced TSA"* may even be considered should dysplasia be present in a TSA.

In conclusion, I completely concur with Dr. Snover that these characteristic tall, eosinophilic cells with penicillate nuclei containing delicate chromatin and nuclear grooves devoid of mitoses, should not be regarded as dysplastic but rather a recapitulation of small intestinal mucosa and "enteric metaplasia" is entirely appropriate.

## References

[1] Snover DC. Diagnostic and reporting issues of preneoplastic polyps of the large intestine with early carcinoma. Ann Diagn Pathol 2019;39:1–14.
[2] Chetty R. Traditional serrated adenoma (TSA): morphological questions, queries and quandaries. J Clin Pathol 2016;68:578–87.
[3] Bettington ML, Chetty R. Traditional serrated adenoma: an update. Hum Pathol 2015;46:933–8.
[4] Sekine S, Yamashita S, Tanabe T, et al. Frequent *PTPRK-RSPO3* fusions and *RNF-43* mutations in colorectal traditional serrated adenoma. J Pathol 2016;239:133–8.
[5] Sekine S, Ogawa R, Hashimoto T, et al. Comprehensive characterization of RSPO fusions in colorectal traditional serrated adenomas. Histopathology 2017;71:601–9.
[6] Hashimoto T, Ogawa R, Yoshida H, et al. Acquisition of WNT pathway gene alterations coincides with the transition from precursor polyps to traditional serrated adenomas. Am J Surg Pathol 2019;43:132–9.

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