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Review Article

BRAF mutation as a potential marker to identify the proximal colon serrated polyps with malignant potential

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Abstract: A large number of serrated polyps with malignant potential in the proximal colon were underestimated using currently available criteria mostly based on architectural and cytological features, contributing to proximal interval colorectal cancers. Recently, increasing evidences indicate that *BRAF*$^{(V600E)}$ mutation is a specific molecular feature and driver of the serrated pathway, and proximal serrated polyps with *BRAF*$^{(V600E)}$ mutation have a high risk of progression to malignancy. We proposed that immunohistochemical detection of *BRAF*$^{(V600E)}$ using a *BRAF*$^{(V600E)}$ mutation-specific antibody is a feasible technique for reproducibly identifying proximal serrated polyps with malignant potential in clinical practice, which may need more aggressive treatment and vigilant clinical monitoring.

Keywords: *BRAF*$^{(V600E)}$ mutation, sessile serrated polyps, microvesicular hyperplasitc polyps, colorectal cancer

Introduction

Although there is a reduction of colorectal cancers (CRCs) in the distal colon because of the use of screening colonoscopy, the incidence and mortality of proximal CRCs have not decreased in recent years [1, 2]. It's believed that a significant proportion of proximal CRCs evolve from the serrated polyp-neoplasia pathway [3]. In clinical practice it is important to identify those serrated precursor lesions with malignant potential in the proximal colon.

Serrated polyps of the colorectum are histologically classified into hyperplastic polyps (HPs), sessile serrated adenoma (SSAs), and traditional serrated adenomas (TSAs) [4]. TSAs are characterized by a predilection for the distal colorectum, and the subsequent cancer risk rate equals that of conventional adenomas [5]. The distinction of TSA from HP and SSA is fairly straightforward because of its epithelial dysplasia.

Recent investigations have revealed that SSAs are high-risk lesions, with a faster progression rate than conventional adenomas [5, 6]. SSAs are mainly found in the right colon, representing 5-25% of serrated polyps [7]. HP was subdivided into three types according to their amount of mucin (i.e., microvesicular, goblet-cell-rich, and mucin-poor). HPs are located usually in the left colon and commonly defined as benign lesions without neoplastic potential [7]. However, recent studies suggested that proximal microvesicular HP (MVHP) may be a precursor to more advanced SSA [4, 8].

Identifying proximal serrated polyps with malignant potential using morphological criteria continues to be a diagnostic problem

There is a scientific controversy about the morphological criteria for the diagnosis of the different serrated polyps. The nomenclature is inconsistent and somewhat confusing because different terms are used. The histological interface between SSA and MVHP continues to be a diagnostic problem using currently available criteria mostly based on architectural and cytological features [9]. There exists a diagnostic "gray-zone" between SSA and MVHP. It's difficult to make an appropriate cutoff for the diagnosis of SSA [9].

Moreover, proper specimen orientation is very important for the differential diagnosis of serrated polyps, which largely relies on architec-

tural changes including the crypt bases [10]. However, routine pathologists could not make a diagnosis frequently because of small biopsy specimens and poor section orientation that did not display the bases of the crypts.

Furthermore, guidelines from USA stated in 2010 that the diagnosis of SSA can be made if a serrated polyp shows 2 or 3 contiguous SSA-type crypts [11]. However, an expert panel recommended recently that serrated polyps with as few as 1 SSA-type crypt should be diagnosed as an SSA [7]. These quickly changing guidelines and recommendations resulted in some confusion among pathologists and gastroenterologists. The interobserver variability in the diagnosis of SSAs may be as high as 40%, even among gastrointestinal pathologists [12]. Some pathologists may have been aware of and accepted these guidelines, whereas others may not. Particularly in developing countries, SSAs were not well recognized by some pathologists and endoscopists [13, 14].

Thus, by using morphological criteria, many proximal serrated polyps are misdiagnosed and categorized wrongly [15]. The frequency of SSA diagnoses varies considerably in the reported literature. Previous studies from Western countries showed that SSAs constitute approximately 2.2-14.7% of all polyps in a large series of patients undergoing colonoscopy for standard clinical indications [9, 16]. In a subset of the Chinese population, SSAs accounted for only 1.0% of all colorectal polyps [14]. Misdiagnosis may lead to an inappropriate management and surveillance for proximal serrated polyps, and thus contribute to proximal interval CRCs. Therefore, it's important to reproducibly identify those serrated polyps with cancer risk, which need more aggressive treatment and vigilant clinical monitoring [6].

It is universally accepted that the determination of a patient's cancer risk on the basis of the morphology of polyps is relied on the identification of dysplasia within the polyp. However, It's difficult to accurately discriminate serrated polyps without traditional cytological dysplasia but with premalignant potential (i.e., SSA and a subset of MVHP) from morphologically similar polyps without cancer risk (i.e., conventional HP) [17]. It might be more appropriate to simply identify this serrated pathway with cancer risk, than discriminate laboriously various subtypes of serrated polyps with great variability.

BRAF$^{(V600E)}$ mutation is a specific molecular feature and driver of the serrated pathway

Serrated polyps are considered to differ not only morphologically, but also in their genetic characteristics from the conventional adenoma-carcinoma sequence [8, 18]. Serrated polyps often exhibit *BRAF* mutation, high level microsatellite instability (MSI-H), and extensive DNA methylation of CpG islands (CIMP-H) [8]. Recently, it has been recognized that *BRAF* mutation are strongly associated with proximal serrated polyps [19]. The most frequent somatic alteration in *BRAF* is a point mutation (*BRAF*$^{(V600E)}$), which results in a markedly increased activity of the protein's kinase domain [20]. This causes enhanced signaling through MEK and ERK, a pathway that controls a wide range of physiologic and tumor-promoting processes.

BRAF$^{(V600E)}$ mutations are frequently present in SSAs (75-90%) [21]. Similar *BRAF*$^{(V600E)}$ mutation frequencies were found in MVHPs, and considered to be a fundamental molecular alteration of MVHP [8]. It's thought that a subset of proximal MVHPs is the precursor lesions of SSAs [4, 8]. Moreover, *BRAF*$^{(V600E)}$ mutations are present in 75-90% of sporadic MSI-H cancers, a frequency that is surprisingly similar to that in SSAs [22]. A recent study found a strong association between *BRAF*$^{(V600E)}$ mutations and serrated hyperplastic aberrant crypt foci (ACF), which might be an early, potentially initiating step on the serrated pathway to cancer [23].

The frequency of *BRAF*$^{(V600E)}$ mutations is relatively lower in conventional HPs (~30-50%) in comparison to SSAs [21]. In contrast, *BRAF*$^{(V600E)}$ mutations rarely occur in classic adenomas [19, 21]. Thus, it could be proposed that *BRAF*$^{(V600E)}$ mutation is a specific molecular feature during the serrated neoplasia pathway.

However, the sequence of *BRAF*$^{(V600E)}$ mutation driving tumorigenesis remained largely speculative. A recent study revealed that Braf$^{(V637E)}$ animals developed sustained hyperplasia, serrated polyps and metastatic carcinomas in intestines [20]. Braf$^{(V637E)}$ in mouse exon 18 is at the orthologous position of the human *BRAF*$^{(V600E)}$ mutation affecting exon 15. The crypt hyperplasia affected nearly every crypt, characterized by focal serrated epithelial formations, which had cytomorphologic features of human microvesicular or goblet cell-rich HPs

[20]. This important study revealed that *BRAF*$^{(V600E)}$ might be the underlying initiating event that is sufficient to induce serrated adenomas and carcinomas in human colon [19].

Immunohistochemical detection of *BRAF*$^{(V600E)}$ might be a feasible technique for reproducibly identifying proximal serrated polyps with malignant potential in clinical practice

As demonstrated above, a deal of serrated precursor lesions with malignant potential in the proximal colon were underestimated using currently available criteria mostly based on architectural and cytological features, contributing to proximal interval CRCs. Recently, increasing evidences indicate that *BRAF*$^{(V600E)}$ mutation is a specific molecular feature and driver of the serrated pathway, and proximal serrated polyps with *BRAF*$^{(V600E)}$ mutation have a considerable high risk of progression to malignancy [10]. Thus, detecting *BRAF*$^{(V600E)}$ mutation as an adjunct diagnostic tool in clinical pathology may reproducibly identify the proximal serrated polyps with cancer risk, which need more aggressive treatment and vigilant clinical monitoring. Moreover, *BRAF*$^{(V600E)}$ could be a target for therapeutic intervention of serrated neoplasia in the colorectum [20].

Determination of *BRAF*$^{(V600E)}$ mutation by direct sequencing was not feasible in routine clinical practice. Furthermore, large number of normal mucosa cells inside the serrated specimens can lead to false-negative results using direct sequencing. Recently, the appearance of a *BRAF*$^{(V600E)}$ mutation-specific antibody made it possible to detect *BRAF*$^{(V600E)}$ protein in routine formalin-fixed, paraffin-embedded specimens of serrated lesions of the colon [10]. This method allows pathologist correlate histomorphology with molecular changes in serrated polyps according to their *BRAF*$^{(V600E)}$ mutation status.

Inclusion, immunohistochemical detection of *BRAF*$^{(V600E)}$ is an applicable technique for reproducibly identifying proximal serrated polyps with malignant potential in clinical practice, which is of great importance to patients, pathologists, gastroenterologists and researchers.

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Disclosure of conflict of interest

None.

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