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Original Article

Bizarre stromal cells of the esophagus polyp or papilloma: clinical and pathologic studiesof nine cases

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Abstract: Bizarre stromal cells (BSCs) are occasionally observed in benign or malignant lesions of the esophagus. We reviewed data from nine cases with BSCs in an esophageal polyp or papilloma. The study cohort included four females and five males with a mean age of 44 (range, 34-54) years. Seven lesions were locatedat the esophagocardiac junction and two in the esophagus. Endoscopic analysis under white light showed that the lesions were polyps or papillomas, and narrow band imaging (NBI) showed that the intra-papillary capillary loops (IPCL) on the surface of the lesion were lost in six cases and normal in three cases. Microscopically, the lesions appeared to be polyps or papillomas. In two cases, the epithelial covering was replaced with a superficial layer of necrotic debris. In seven cases, the epithelial covering showed hyperplasia, but not dysplasia. In all cases, BSCs were scatteredin the lamina propria. The BSCs were mostly located beneath the epithelial covering or superficial layer of necrotic debris in rows parallel to the blood vessels and vertical to the mucosal surface. The BSCs were positive for vimentin, but negative for CKpan, CD34, CD68, CD163, actin, desmin, S-100, DOG1, and HMB45. The presence of BSCs in anesophageal lesion may lead to misdiagnosis. Endoscopic, microscopic, and immunohistochemical characteristics are helpful to arrive at an accurate diagnosis.

Keywords: Bizarre stromal cells, esophagus, intra-papillary capillary loops, narrow band imaging

Introduction

The prevalence of gastrointestinal (GI) cancer in China is one of the highest worldwide, thus early detection and treatment are important measures to prevent the continued increase in the incidence of this disease. With the recent development of narrow band imaging (NBI) and corresponding intra-papillary capillary loop (IPCL) technology [1-3], precancerous lesions of the GI tract can be detected early and resected via endoscopy submucosal dissection (ESD). Although the use of this technology can inhibit the progression of early precancerous lesions to invasive carcinoma, the rate of misdiagnosis with this technology has tended to increase.

Benign lesions, due to inflammation, polyp, or papilloma formation, are more commonin the GI tract than in other organs. These benign lesions often include bizarre stromal cells (BSCs), which present an important diagnostic pitfall [4-7], since they can closely resemble a malignancy, thus leading to significant overtreatment. In the present study, we compared endoscopic, microscopic, and immunohistochemical characteristics of BSCs in esophagealpolyps and papillomas to help distinguish these features from carcinomas and other malignant tumors.

Materials and methods

Patients and tissue specimens

We retrospectively reviewed clinical data from the medical records of nine patients diagnosed with a papilloma or polyp with BSCs attheesophagocardiac junction (ECJ) who were treated at the Department of pathology, Affiliated Tumor Hospital of Guangxi Medical University and the Department of Pathology of the Peoples' Liberation Army 152nd Hospital. Hematoxylin and eosin-stained slides were available for all cases.

Table 1. Summary of clinicopathological features

No	Age	Sex	Symptoms	Location	Surgical Procedure
1	50	F	Abdominal distension	ECJ	B and ESD
2	39	M	Sour regurgitation	ECJ	B and ESD
3	34	M	Abdominal distension	ECJ	B and ESD
4	48	F	Belching	E	B and ESD
5	54	M	Heartburn and belching	ECJ	B and ESD
6	36	F	Abdominal distension	ECJ	B and ESD
7	52	M	Abdominal distension	ECJ	B and ESD
8	46	M	Heartburn	E	B
9	40	F	Abdominal distension	ECJ	B

F, female; M, male; E, esophagus; ECJ, esophagocardiac junction; ESD, endoscopy submucosal dissection; B, biopsy.

Endoscopy examination

All cases were first examined under white light and then by NBIusing an EVIS LUCERA ELITE CV-290Video System Centre (Olympus Corp., Tokyo, Japan).

Immunohistochemical analysis

Representative serial sections for immunohistochemical analysis were available for each case. Immunohistochemical analysis was performed using the BOND-MAX Automated IHC/ISH Stainer (Leica BiosystemsGmbH, Wetzlar, Germany). The primary antigens including: Actin (HHF35), CD163 (10D6), CD34 (QBEnd/10), CD68 (514H12), CKpan (AE1/AE3), Desmin (DE-R-11), HMB45, S-100, Vimentin (V90), Ki-67 (MIB-1), DOG1 (K9), P53 (Do-7). All the antigens were purchased from Maxin-Bio Co. (Fuzhou, China).

Results

Clinical findings

The patient cohort included five males and four females with a mean ageof 44 (range, 34-54) years at the time of diagnosis. The most common clinical symptoms included abdominal distension, sour regurgitation, belching, and heartburn (**Table 1**).

Endoscopic examination results

Endoscopic analysis under white light revealed an abundance of polyp-like structures in the esophagus (**Figures 1A** and **2A**). NBI showed clear IPCLs in some cases, while other cases had no IPCLs and unclear surfaces (**Figures 1B**, **2B** and **2C**). Normal IPCLs were presenton the lateral esophagus (**Figures 1B**, **2B** and **2C**).

Macroscopic features

Each case showed a well-demarcated lesion. The lesions contained an abundance of polyp-like structures (**Figure 2D**). The average lesion diameter was 1.2 cm (range, 0.8 to 1.6 cm).

Microscopic features and immunohistochemistry results

In case 1 and case 3, the epithelial covering of the mucosa was replaced with robust granulation. In the remaining sevencases (case 2, and cases 4-9), the lesions were covered with stratified squamous epithelium with hyperplasia, but no dysplasia (**Figures 3A**, **4A** and **5A**).

In all cases, BSCs were scattered in the lamina propria. The BSCs were mostly located beneath the epithelial covering or superficial layer of necrotic debris in rows parallel to the blood vessels and vertical to the mucosal surface (**Figure 3B-D**). However, in biopsy specimens from case 2, histological examinations showed dysplastic spindle cells in the lamina propria and hyperplasiaof the stratified squamous epithelium (**Figure 4**), suggesting carcinoma. The lesionswere papillomas or polyps; therefore, ESD was performed to arrive at a definitive diagnosis and to choose an appropriate treatment strategy. Histological examination of the resectedspecimens (**Figure 5**) revealed the presence of BSCs within the lamina propria (**Figure 5B** and **5C**), which ranged fromelongated spindle cells to stellate cells to large round cells with abundant amphophilic cytoplasm, vesicular nuclei, and large eosinophilic, inclusion-like nucleoli (**Figure 5B** and **5C**). In some specimens, the cells blended into the granulation tissue. Multinucleated and giant cell forms were also observed. Rarely, atypical pale epithelioid cells formed round, cohesive clusters resembling acini or vascular structures. Mitotic figures were uncommon and no atypical mitoses were identified.

Immunohistochemically, the tumor cells were positive forvimentin, but negative for endothelial monocyte antigen, cytokeratin 14, cytokeratin AE1/AE3, CD68, HHF-35, desmin, S-100,

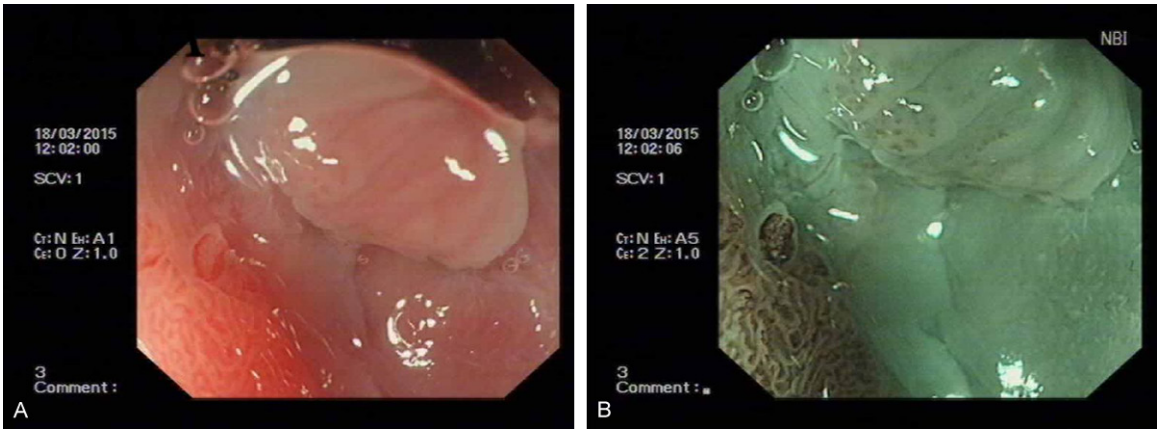

Figure 1. A. A lesion located in the EGJ, as observed with white light. B. By NBI, the IPCLs of the surface of the lesion appeared normal.

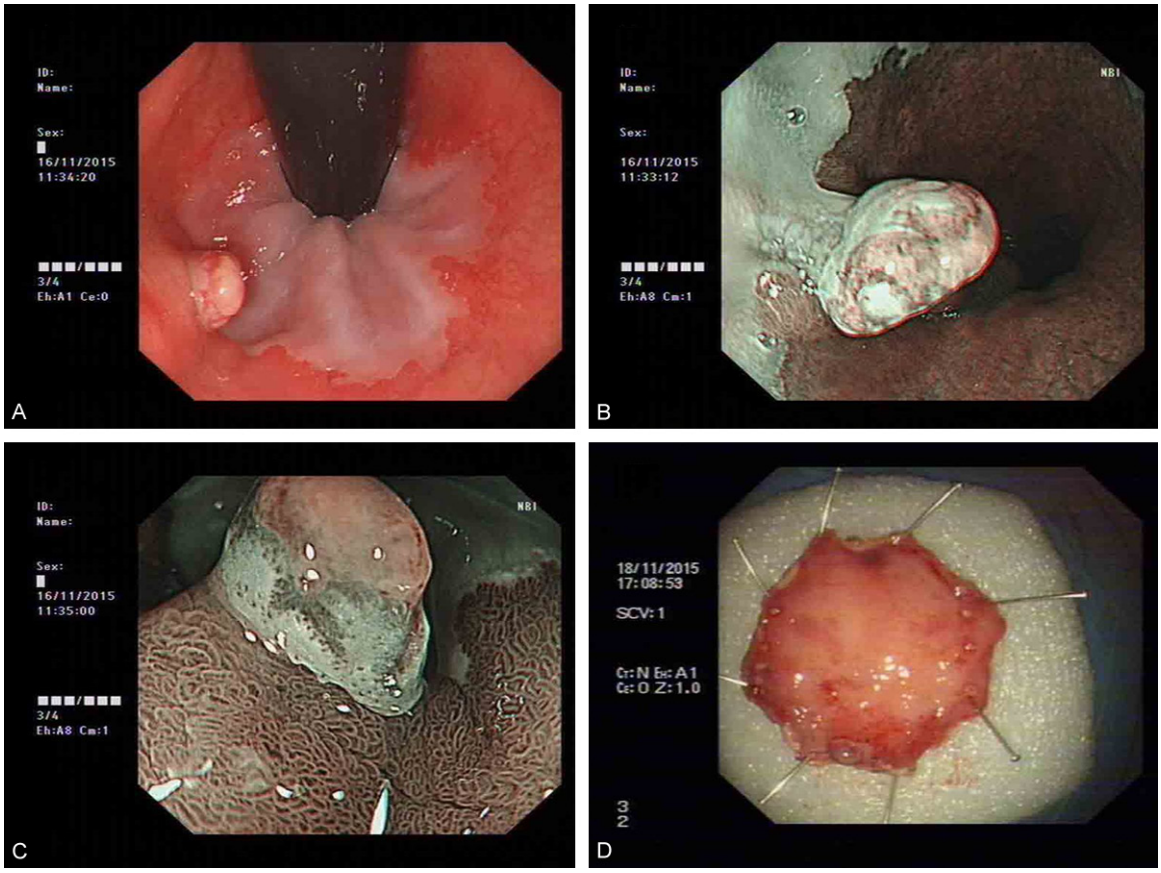

Figure 2. A. Under white light, polyp-like lesions were observed at the EGJ. B. NBI was insufficient to observe IPCLs on the lesion surface. C. However, the presence of IPCLs on the lateral lesion was observed. D. An ESD specimen with a polyp-like lesion.

CD34, CD163, and HMB45. Ki-67 positivity was < 1%, indicating a low proliferative rate. Based on these histopathological and immunohistochemical findings, a diagnosis of pseudomalignant erosion of an inflammatory polyp or papilloma was made.

Discussion

BSCs are not uncommon in the GI tract [4-7], breast [8-10], and other sites [11-14]. The presence of these BSCs in small specimens, such as biopsy specimens, may be misinterpreted as

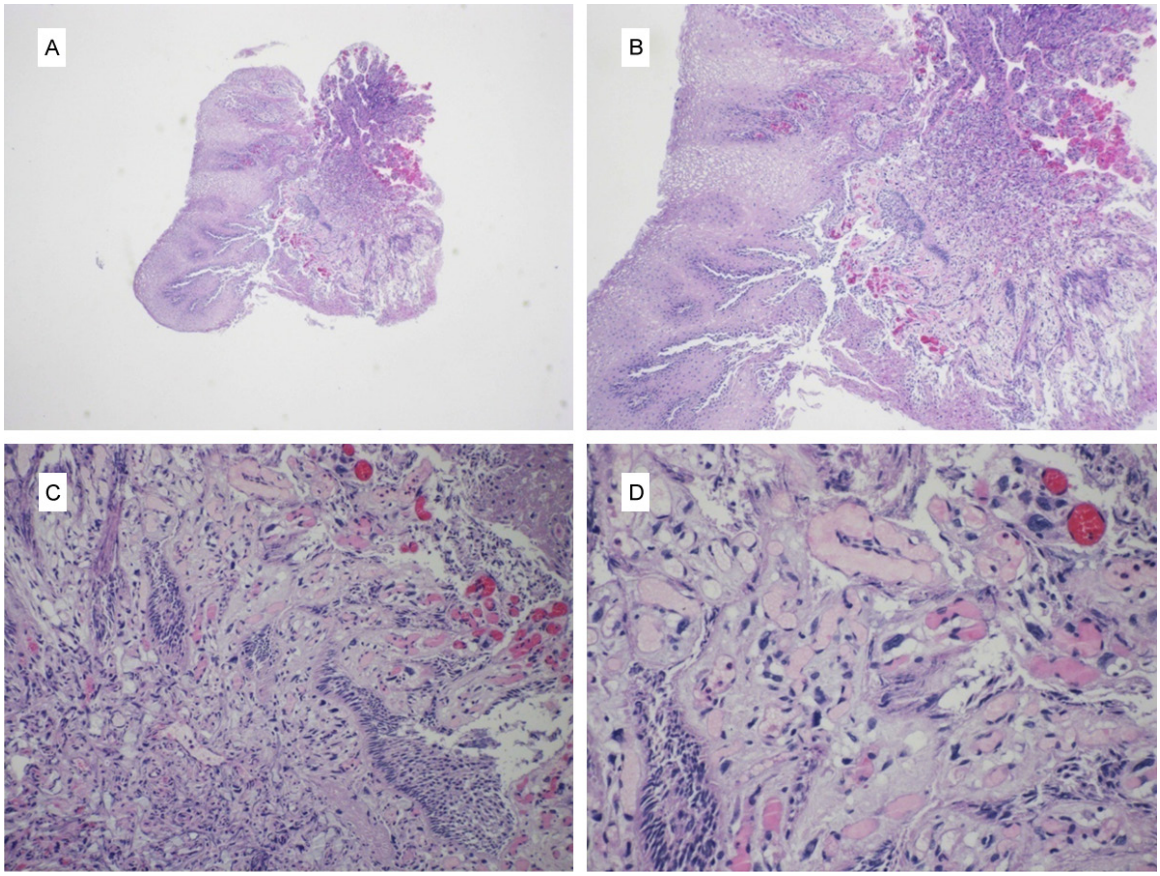

Figure 3. Biopsy specimen. A and B. No dysplasia of the epithelial covering was observed. C and D. The BSCs were scattered in the upper portion of the lamina propria. The BSCs were parallel to the blood vessels and vertical to the mucosal surface.

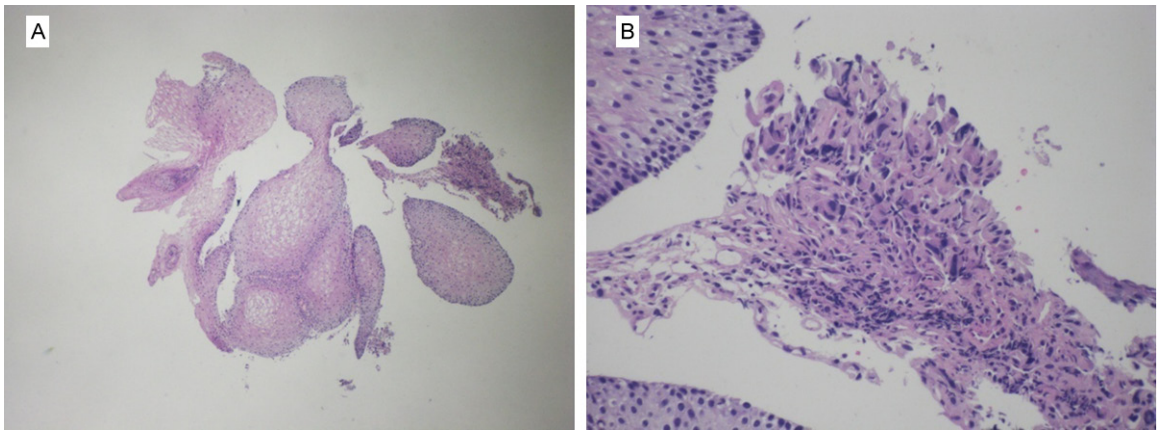

Figure 4. Biopsy specimen. A. BSCs were observed beneath the epithelial covering. B. The BSCs had dysplasia and had no polarity.

asarcomatous or carcinomatous malignant process [4-5, 7, 10]. Awareness of the existence of these benign, but bizarre-looking, giant cells may prevent such diagnostic pitfalls and help to relieve patient pain.

Shekitka et al. [6] reported 33 cases of BSCs in polyps and ulcers of the GI tract in a study oftwo esophageal and four gastroesophageal specimens. To date, at least 20 cases of pseudosarcomatous lesions in the esophagus have

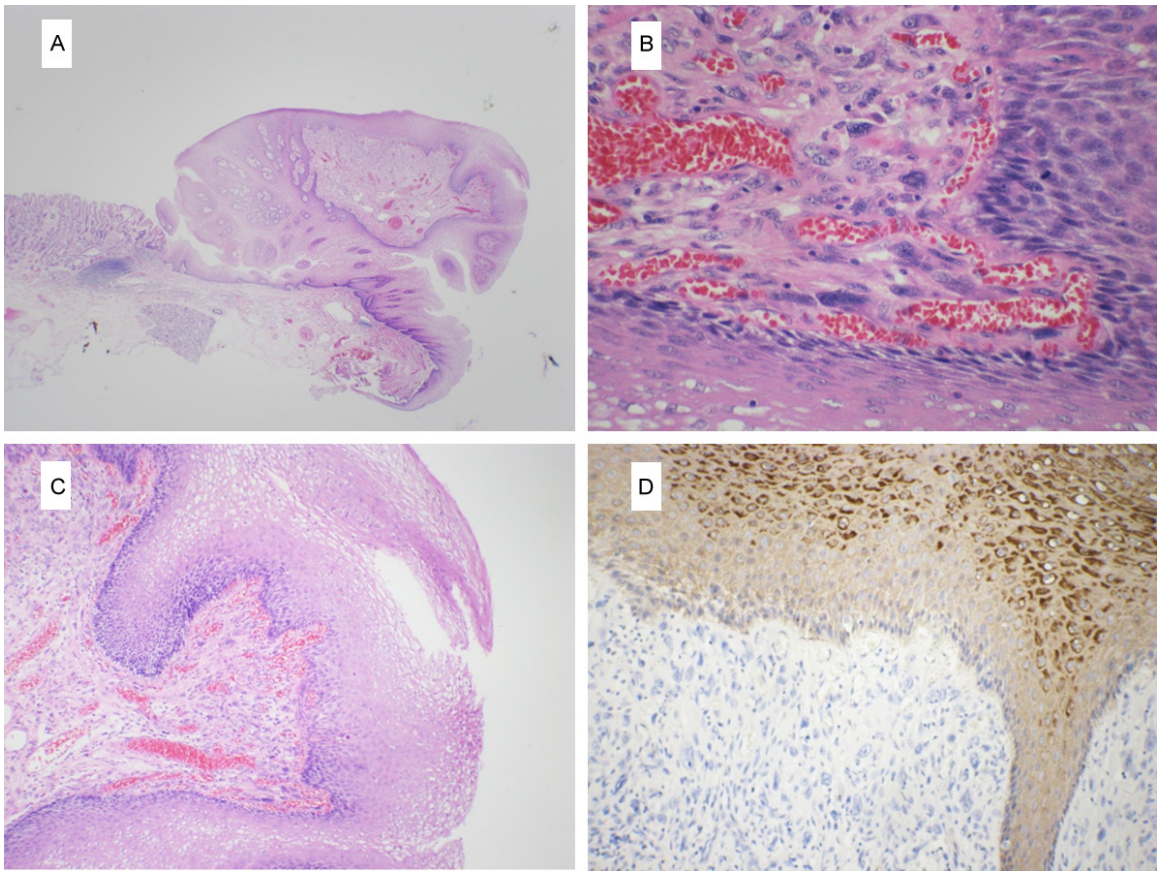

Figure 5. ESD specimen. A. A papilloma in the ECJ. B. No dysplasia of the epithelial covering was observed. C. The BSCs were scattered in the upper portion of the lamina propria. D. The BSCs were negative for CKpan.

been reported and most were located at the ECJ [5-7, 15-17].

Of the nine cases included in the present study, BSCs were observed at the ECJ in seven cases and in the esophagus in two cases. In the English literature, most BSCs in the esophagus-were located at the ECJ. Patients typically presented with unspecific characteristics, such as abdominal distension, sour regurgitation, belching, and heartburn. Endoscopic observation and under white light revealed an abundance of polyp-likestructures in the esophagus. NBI showed that some cases had clear IPCLs, while others had no IPCLs and the surfaces were unclear. However, we were able to observe normal IPCLs in the lateral esophagus.

Some biopsy specimens were histopathologically diagnosed as dysplasia or suspected as carcinoma or sarcoma; therefore, ESD was performed. The ESD specimens showed that some of the epithelial covering was replaced with a superficial layer of necrotic debris with scattered BSCs underneath. In some cases, the epithelial covering was retained with only mild hyperplasia, but no dysplasia, in addition to scattered BSCs underneath. These BSCs only expressed vimentin, but not S-100, actin, desmin, CKpan, CD68, CD163, HMB45, p53, or CD34. Ki-67 positivity was < 1%, indicating a low proliferative rate. Together, these results excluded a diagnosis of sarcoma or carcinoma. Since BSCs are differentiated from malignant tumors, there should be no misdiagnosis as carcinoma, especially in a biopsy specimen. In our cohort, two cases were suspected carcinoma because the stromal cells had irregular shapes and nuclei with some hyperplasia of the covering squamous epithelium. Moreover, some morphological irregularities were observed in glands and blood vessels by endoscopy under white light and NBI. The presence of BSCs can be misdiagnosed as spindle sarcoma, such as leiomyosarcoma, or a GI stromal

tumor. Of course, such lesions can be misdiagnosed as malignant melanoma. To diagnose this lesion correctly the pathologist should perform endoscopic evaluation of the IPCLs. In most cases, the IPCLs are normal, indicating that the lesion is not malignant. In rare cases, no IPCLs are observed, leading to a suspicion of a malignant lesion. Nonetheless, the lateral-lesion must be assessed, where there is always normal IPCLs. From a histopathological view, the epithelial covering should be assessed to determine whether the epithelial covering is characteristic of dysplasia. If dysplasia is absent from the epithelial covering, a diagnosis of malignancyis contraindicated. If the epithelial covering shows characteristics of dysplasia, the epithelial covering and BSCs should be evaluated to determine if they share the same cytoplasmic and nuclear characteristics. In this study, we also evaluated the stromal cells. BSCs sometimes appeared singularly, but none displayed dysplasia or mitosis. It is also important to assess the distribution and growth patterns of BSCs, which are mostly located beneath the epithelial covering or the superficial layer of necrotic debris. Also, BSCs grow parallel to blood vessels and vertical to the mucosal surface. Finally, it is very important to evaluate the immunochemical characteristics of BSCs. In this study, BSCs were positive for vimentin, but negative for CKpan, desmin, CD117, DOG1, S-100, CD68, actin, CD34, CD163, and p53, while Ki-67 positivity was low. Taken together, these results indicate that these cells were the reactive component of the lesion.

Although the histogenesis of BSCs remains obscure and controversial, some histopathological reports indicate that vimentin positivity is strongly suggestive of a myofibroblastic origin [18]. Abd el-All [19] investigated the histopathological and immunohistochemical features of breast spindle cell tumors, and suggested that vimentin/CD34-positive fibroblasts in mammary stroma could result from differentiation of pluripotent mesenchymal precursor cells with the potential to differentiate into several mesenchymal lines. In our study, the BSCs were only positive for vimentin and negative for actin, desmin, CD34, CD68, CD163, S-100, and HMB45, indicatinga possible origin from myofibroblasts/fibroblasts. As we know, granulation tissue is composed by the proliferation of fibroblasts, inflammatory cells, and edema of numerous newly formed, thin-walled, delicate capillaries. From a histopathological view, BSCs are mostly located beneath the epithelium or the ulcer and vertical to the mucosal surface, and parallel to the blood vessels. Taken together, these characteristics indicate that BSCs may originate from myofibroblasts/fibroblasts.

Disclosure of conflict of interest

None.

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