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CASE REPORT

Adenosquamous carcinoma of the right colon with diffuse signet-ring mucinous component

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Abstract
Colorectal carcinoma is one of the most frequent human malignant neoplasms. Besides the most common histological types, colorectal adenosquamous carcinoma is very rare, being microscopically constituted by tumoural glandular and squamous components. The diagnosis of primary colon adenosquamous carcinoma requires the exclusion of a metastatic squamous cell carcinoma and the extension of a primary squamous cell carcinoma from the anal–rectum junction. We report a case of primary adenosquamous carcinoma of the ascending colon in a 62-year-old Caucasian man affected by long-standing ulcerative colitis. Peritumoural lymph nodes and distant metastasis were present. We reported also a diffuse signet-ring mucinous component, which has not been previously observed. Moreover, we investigated microsatellite and all-RAS/B-RAF status, p16 and p53 protein expression, and the molecular presence of human papillomavirus DNA in all the morphologically distinct components, in order to suggest pathogenetic factors influencing the aggressive prognosis of colon adenosquamous carcinoma.

Keywords Adenosquamous carcinoma · Microsatellite stability · p16 protein · Right colon · Signet-ring cells

Introduction

Colorectal carcinoma is one of the most frequent human malignant neoplasms, being the third as frequency after breast and lung cancers [1]. Colorectal carcinoma displays several histological types and adenocarcinoma represents 86% of cases, followed by squamous cell carcinoma and mucinous carcinoma [2]. Colorectal adenosquamous carcinoma (ASC) is very rare and accounts for approximately 0.03–0.18% of all colorectal cancers [3]. Histologically, ASC is constituted by two malignant components: glandular, with various grade of differentiation, and squamous cell counterpart, with horny pearls and intercellular bridges. Based on how those two components intermingle, ASC is classified into composite, characterized by haphazard mixture of them, and collision type [4]. The latter shows clearly distinct and adjacent adenocarcinomatous and squamous cell carcinomatous areas [5]. Surgical resection is the gold-standard therapy for colorectal ASC. The role of adjuvant radiotherapy and chemotherapy is still debated, because of the rarity of this neoplasm, but is suggested in cases with lymph node metastasis [4, 6]. In fact, patients with negative lymph nodes have similar prognosis of those with adenocarcinoma, while, in case of nodal involvement, the outcome of ASC is worse [7]. We observed a case of ASC with a diffuse signet-ring mucinous component, not previously reported in this type of colon carcinoma.

Case report

A 62-year-old man with long-standing history of ulcerative colitis (UC) and recent worsening of general conditions (frequent bloody evacuations, asthenia, and weight loss)

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was subjected to a coloscopy one year ago in our Hospital. During endoscopic procedure, it was possible to explore the gut from the anus to the ascending colon (80 cm from the anal margin), where a tight stenosis, consisting in a friable and ulcerated lesion, prone to bleed with the contact of the endoscope, was present (Fig. 1a, b). The remnant colorectal mucosa appeared hyperaemic and oedematous (Fig. 1c). Pathological examination of the lesion revealed an adenocarcinomatous infiltration, with signet-ring and extracellular mucin-lake aspects. Successively, an eco-endoscopic procedure revealed multiple lymph adenopathies in the mediastinum and hepatic hilum. Biopsy examination revealed adenocarcinomatous infiltration morphologically similar to the colonic tumour biopsies. Patient was discussed at multidisciplinary team meeting with the oncologist, radiologist, and surgeon, for management plan. Given the mediastinal and hepatic lymph nodes metastases, pre-operatory clinical stage was at least Stage IVA. However, the patient was referred for radical surgical resection, for his history of UC and the presence of right-colon adenocarcinoma. Pre-operatory total body TC scan revealed multiple loco-regional and non-regional lymph adenopathies and peritoneal free fluid and laboratory tests showed anaemia (Hb 7.4 g/dL), piastrinopenia (94 mile/μL) and increased levels of oncomarkers CEA (> 1005 ng/mL) and CA 125 (44.9 IU/mL). The operation consisted of a subtotal colectomy with central vascular ligation. Intraoperatively, the tumour looked clearly in an advanced stage with infiltration of the visceral peritoneum; a wide excision was carried out and, after reconstruction, a diverting ileostomy fashioned. Gross examination of the surgical specimen revealed a 7 cm stenosing and ulcerated lesion of the right colon, infiltrating the visceral wall for the full thickness. Histological examination (Fig. 2) demonstrated microscopic features typical of composite-type ASC. Immunohistochemically, the tumour cells resulted CK20+, CDX-2+, CK7+ and CK5/6− in glandular/mucinous component and CK5/6+ in the squamous one. The tumour was extended to the visceral peritoneum and displayed extracellular mucin-lake and signet-ring cells component, invading also the surface of the appendix. Tumour infiltrating lymphocytes were almost absent, except around the squamous component, where there was a non-brisk lymphocytes infiltration. Immunohistochemical evaluation of mismatch repair (MMR) genes demonstrated MLH1 (60% positive), MSH2 (90% positive) and MSH6 (more than 95% positive) staining of the tumour nuclei of the glandular/mucinous components, resulting in microsatellite stability (MSS). Immunostaining for p53 protein revealed overexpression only in the mucinous component of ASC. Moreover, we tested immunohistochemically the expression of p16 protein, which stained strongly and diffusely all tumour components (Fig. 2). The detection of human papillomavirus (HPV) DNA, evaluated by pyrosequencing technology, was negative in both glandular and squamous components. The mutation status of all-RAS (exons 2, 3, and 4) and B-RAF gene (exon 15) was evaluated, but no alteration of those genes was detected. All the twelve peritumoural sampled lymph nodes were metastatic, with glandular and signet-ring cells aspects (Fig. 3).

Fig. 2 Colonic adenosquamous carcinoma: microscopic and immunohistochemical features. **a** Composite-type adenosquamous carcinoma, invading the visceral peritoneum. **b–d** The neoplasm shows distinct adenocarcinomatous, with mucin-lake and signet-ring cells component, and squamous cell carcinomatous aspects (Haematoxylin–Eosin stain. Original magnification: **a** 40×; **b–d** 200×. **e–h** Immunohistochemical p16 staining of adenosquamous carcinoma. Strong and diffuse staining in all the components of our case of adenosquamous carcinoma, with somewhat lower expression in the signet-ring part (original magnification **e** 40×; **f–h** 200×) ▶

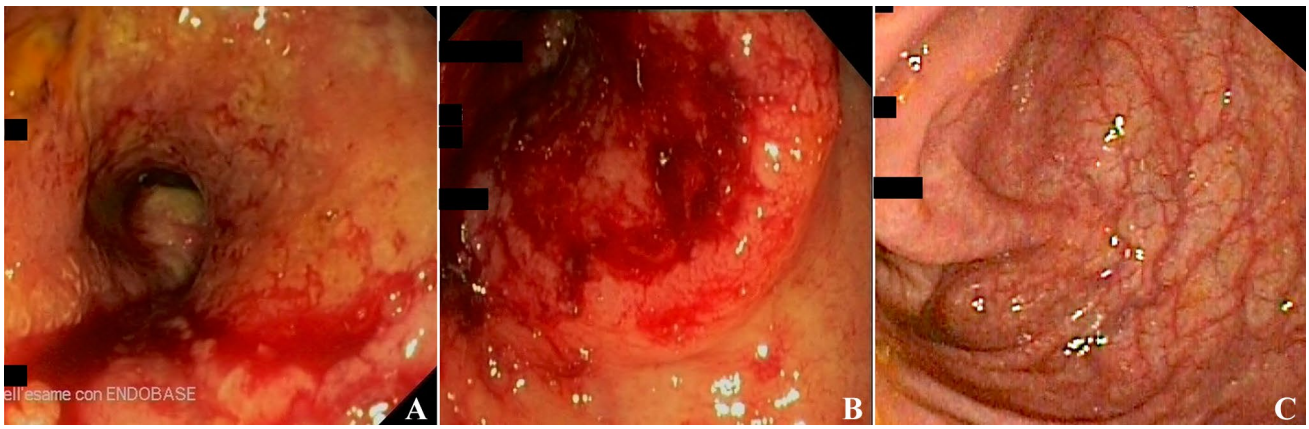
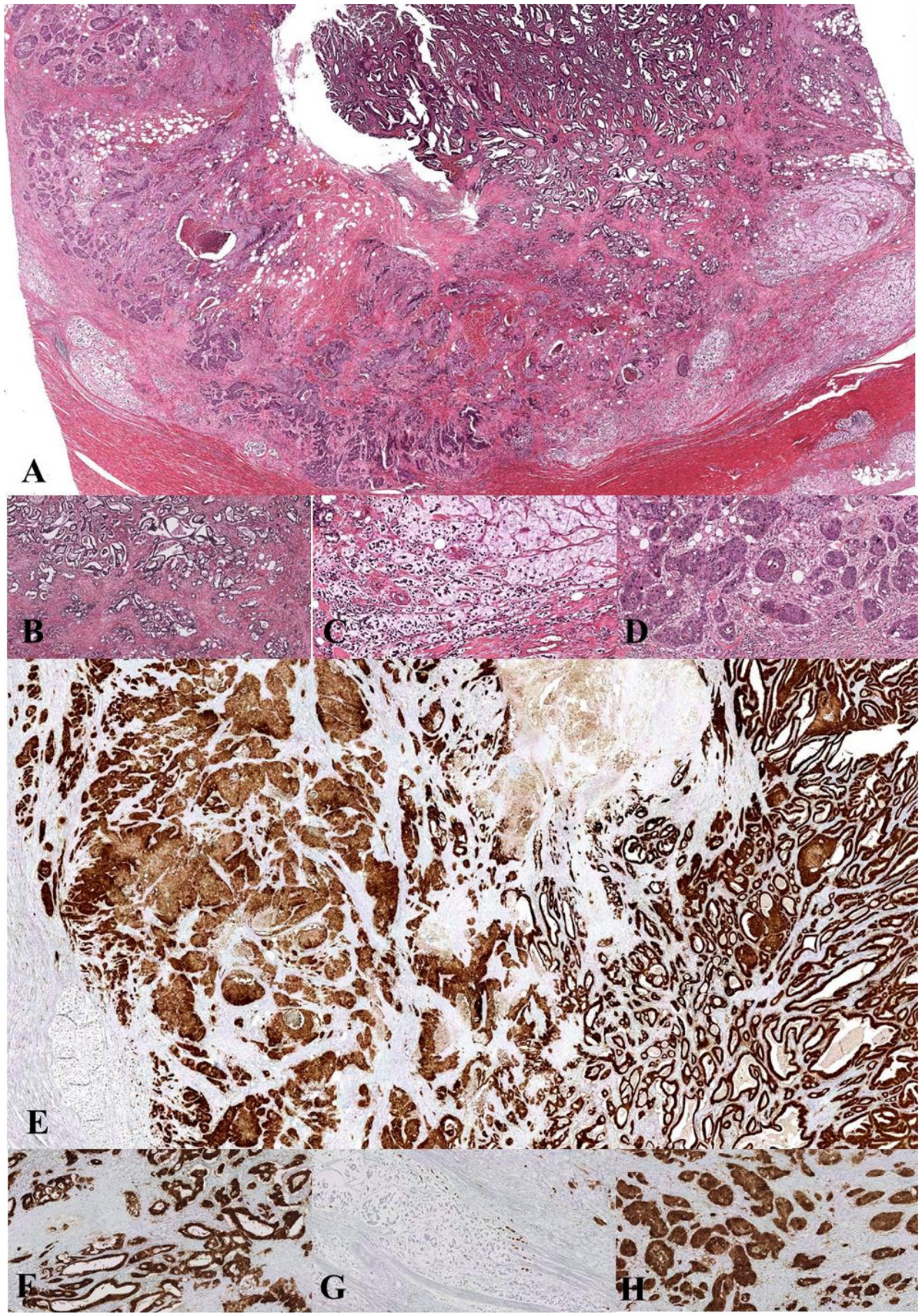


Fig. 1 Endoscopic images of adenosquamous carcinoma of the ascending colon and remnant colonic mucosa. **a**, **b** Ulcerated mucosal lesion stenosing the lumen of the colon. **c** Surrounding hyperaemic and oedematous mucosa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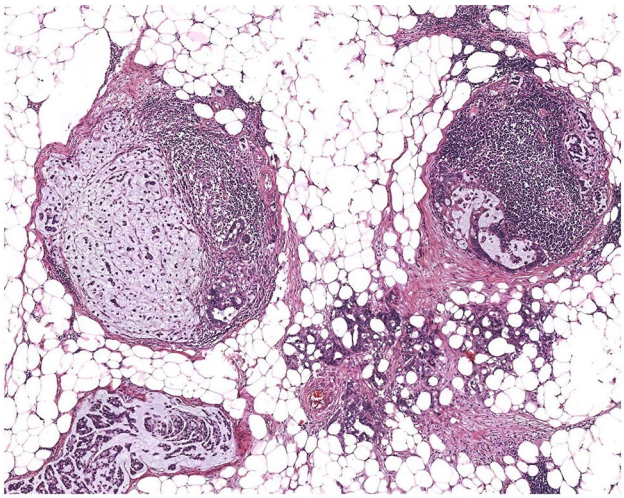

Fig. 3 Lymph nodes metastasis from adenosquamous carcinoma. Peritumoural nodes examination reveals metastasis with glandular/signet-ring mucinous, but not squamous, aspects (Haematoxylin–Eosin stain. Original magnification: 40×)

Lymphatic and venous invasions were also present. Signet-ring cells deposits were present in the pericholecystic and omental adipose tissue, and pTNM classification of the tumour was pT4bN2bM1c. The remaining colonic mucosa had typical aspects of long-standing UC, in remission phase, with focal low-grade dysplasia (Fig. 4). After the surgery, patient's recovery was uneventful, but he died several weeks later for a heart attack consequent to cachexia induced by neoplastic and metastatic disease.

Discussion

Primary ASC of the colon and rectum is a rare neoplasm, described firstly by Herxheimer in 1907, referring to it as *cancroide* [8]. The histogenesis of ASC is still unknown and several hypothesis have been suggested: (1) foci of ectopic squamous cells of the intestinal mucosa may undergo neoplastic transformation; (2) uncommitted mucosal cells at the basal part of the crypt may transform directly into squamous malignant cells; (3) normal or neoplastic glandular component may be transformed and gave origin to malignant squamous neoplasm [4]. In our experience, squamous metaplasia is not an uncommon finding in adenomatous polyps of colon–rectum, but its pathogenesis remains uncertain. It has been proposed that some conditions (UC, schistosomiasis, radiation, HPV infection), stimulating abnormally and repeatedly colonic mucosa, may influence and stimulate metaplastic process [9]. In particular, long-standing chronic inflammation, regardless of clinical activity, is likely to stimulate aberrantly the differentiation of uncommitted cells to squamous epithelium [9]. Persistent microscopic mucosal inflammation, also without evident clinical or endoscopic anomalies, is a common report during UC [10]. There are no data specifically evaluating a relationship between UC and ASC development. Nevertheless, being the risk factors involved in the development of mucosal metaplasia the same reported for the progression of colorectal adenocarcinoma (i.e. the duration and extent of the disease and grade of inflammation), we can speculate that, for the same reason, there is a relatively higher incidence of ASC in

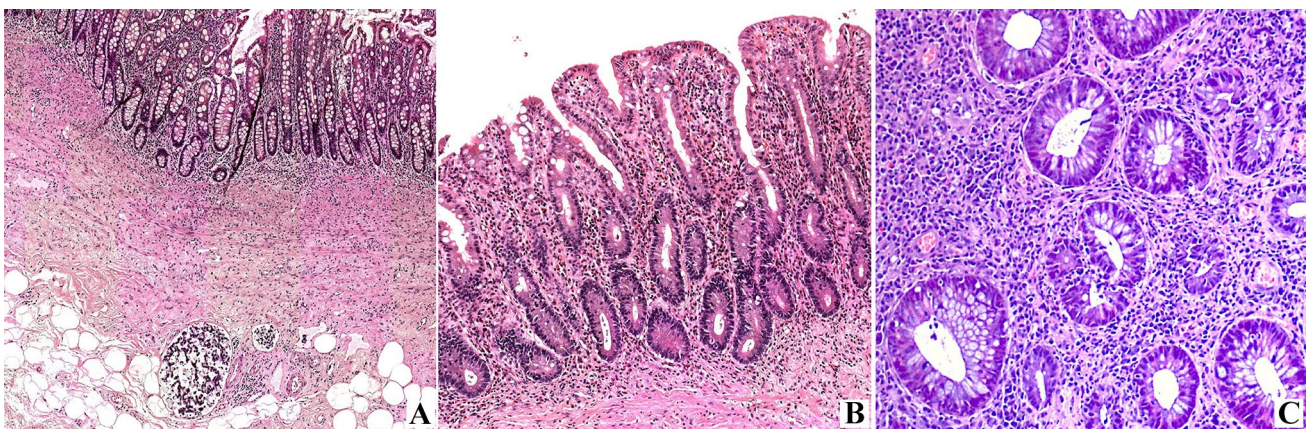

Fig. 4 Ulcerative colitis: microscopic findings. **a**, **b** Remission phase of ulcerative colitis is characterized by architectural distortion of the colonic crypts, chronic inflammation of the *lamina propria*, with eosinophilic granulocytes, basal plasmocytosis and Paneth cell metaplasia in left colon and rectum. The *muscularis mucosae* is thickened. In **a**, it is shown neoplastic lymphangitis by the signet-ring mucinous component of adenosquamous carcinoma. **c** In this biopsy specimen, collected several years ago in our patient, it is demonstrated the active phase of his ulcerative colitis. It is shown severe interstitial lymphoplasmacellular inflammation in association with intra-epithelial neutrophilic granulocytes (Haematoxylin–Eosin stain. Original magnification: **a** 40×; **b** 100×; **c** 200×)

association with UC. The diagnosis of primary ASC of the colon should be avoided in tumours located less than 8 cm from the dentate line and requires to rule out local extension or colonic metastasis from squamous cell carcinoma of other sites [3]. Although clinical presentation is similar to classic colon adenocarcinoma, ASC has a greater metastatic potential and a more aggressive clinical course [6, 7]. In our knowledge, this is the first case reported in literature in which a diffuse signet-ring cells component is detected. The latter, although present in a small amount, has been reported to worsen the prognosis [11]. The role of microsatellite instability (MSI) in the pathogenesis of ASC is still unclear. MSI is determined by defects in MMR genes. Instability at one locus is considered low grade, while at two or more loci is considered a high-grade instability. According to the WHO 2010 classification, mucinous colorectal cancer is considered low grade when has MSI, whereas those with MSS are high grade [12]. HPV has been detected in squamous cell carcinoma of several anatomic sites. The role of HPV in the pathogenesis of colonic ASC is still debated. Positive immunohistochemical screening for p16 protein may suggest HPV infection, but it needs a molecular confirmation [6]. In our case, negative HPV DNA detection suggests other mechanisms responsible of tumour p16 overexpression. The $p16^{INK4a}$ gene is reported to inhibit cyclin D1 and its catalytic subunits cyclin-dependent kinases (Cdks) 4/6 in the cell-cycle, blocking the cell progression from G1 to S phase and, therefore, preventing retinoblastoma tumour suppressor phosphorylation mediated by Cdk4 [13]. The positive proliferative stimulus mediated by cyclin D1 and Cdk4 likely causes a positive feedback, with a consequent $p16^{INK4a}$ overexpression and uncontrolled cell growth [14]. The treatment of choice for primary colon ASC is the radical surgical resection. However, when this approach is not viable for particular characteristics of the tumour (location, extension, etc.), neoadjuvant/adjuvant chemotherapy is administered [4, 6]. The prognosis of colon ASC is worse than classic adenocarcinoma and is influenced by several factors, firstly the presence of lymph node and/or extra-nodal metastasis, the right-sided location and the history of UC.

Primary colonic ASC is a very rare entity and early diagnosis and surgical treatment are essential to improve clinical outcome. We describe, for the first time, a composite-type colon ASC with a diffuse signet-ring mucinous aspect, likely worsening the prognosis. Further histogenetic investigation and improvement of post-surgical adjuvant therapies are auspicable in order to reduce mortality of this aggressive malignant neoplasm.

Author contributions MDP and FB conceived and designed the work, and wrote, edited and reviewed the manuscript. MF and GB collected data, and wrote, edited, and reviewed the manuscript. ED, GS, GP, and AO researched and analysed data, and wrote, edited, and reviewed the manuscript. All Authors gave final approval for publication and take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interests.

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