Case Report

Lymphoepithelioma-like carcinoma of the colon

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Abstract: An 85-year old female had a polyloid tumour in the sigmoid colon that histologically conformed to a lymphoepithelioma-like (LEL) carcinoma. The tumour was arranged in cords, chains, clusters and microalveoli of pleomorphic, irregular cells set within a dense intratumoral lymphocytic stroma. The tumour was EBV-negative and showed loss of MLH-1 and PMS-2 mismatch repair proteins. The patient did not fulfil the criteria for HNPCC. Only 5 other cases of primary colon LEL carcinoma have been described previously and only one case appears to have an unequivocal association with EBV. In addition, one of the cases was encountered in a HNPCC patient. This is an unusual morphologic variant of a microsatellite unstable tumour with a LEL pattern, not associated with EBV.

Keywords: Lymphoepithelioma-like carcinoma, medullary carcinoma, mismatch repair proteins, EBV, intratumoral lymphocytes, microsatellite instability

Introduction

Lymphoepithelioma-like (LEL) carcinomas are defined as tumours with histological similarity to nasopharyngeal carcinoma [1]. As such these tumours accompanied by a lymphoid stroma, small nests of cancer cells which are uniformly distributed throughout the lymphoid stroma and a sharp demarcation between the tumour nests and the non-desmoplastic lymphocyte-rich stroma, which often times resembles lymphoid tissue [2]. The other interesting association of these tumours, especially nasopharyngeal carcinomas, is with Epstein-Barr virus (EBV). Examples of LEL carcinoma have been encountered in multiple sites outside of the nasopharynx: lung, salivary gland, skin, thymus, GIT (especially the stomach), prostate, etc.

The best recognized example of LEL carcinoma in the GIT occurs in the stomach. Lymphoepithelioma-like gastric carcinoma is a rare type of gastric carcinoma, was first described by Watanabe et al in 1976 as “gastric carcinoma with a lymphoid stroma” [3]. Subsequent reports using the synonyms: undifferentiated carcinoma with lymphoid stroma, gastric lymphoepithelioma-like carcinoma or medullary carcinoma, all describe carcinomas with similar morphology.

Thus far, only 5 cases of LEL carcinoma have been documented in the colon and the association with EBV has been inconsistent [4-8]. In addition, the MSI status has not been explored in all reported cases.

The purpose of this paper is to highlight this very unusual variant of colon cancer, discuss its putative association with EBV and also discuss the role of mismatch repair proteins in LEL carcinoma of the colon.

Clinical features

An 85-year old patient presented with change in bowel habit and endoscopy was performed to elucidate the cause. A tumour was visualised but the biopsy was negative. Based on the endoscopy and imagining, the patient had an abdomino-perineal resection. Six months after the operation, she remains well with no evidence of recurrent disease.

Material and methods

The specimen was received in 10% neutral buffered formalin, opened and fixed as per departmental grossing protocol for colon resections. Formalin fixed sections were routinely processed generating hematoxylin and eosin stained
sections. Immunohistochemistry was performed on the formalin fixed sections using the streptavidin biotin complex technique with commercially available antibodies following microwave antigen retrieval. The following antibodies were used: cytokeratin, CK7, CK20, epithelial membrane antigen (EMA), estrogen receptor (ER), progesterone receptor (PR), CDX-2, chromogranin, synaptophysin, p53, EBV-LMP and the four mismatch repair proteins: MLH-1, MSH2, PMS-2 and MSH-6. In addition, Epstein Barr virus encoded small RNAs was sought by in-situ hybridisation (EBER-ISH).

Results

Gross pathology: The resection specimen consisted of two lengths of bowel: 140mm and 80mm and within the former piece the tumour was noted. Within the posterior wall of the sigmoid colon a polypoid but sessile tumour measuring 42 x 30 x 15mm was present. The tumour was pink-tan in colour and was sampled in total.

Microscopy: The polypoid nature of the tumour was confirmed (Figure 1) and it was composed of tumour cells arranged in clusters, trabeculae or cords, chains, small tubules and in single cells within a dense lymphocytic background (Figure 2). Individual tumour cells were large, pleomorphic with abundant eosinophilic cytoplasm, large vesicular nuclei, irregular nuclear profiles and prominent nucleoli (Figure 3). The lymphocytic component was mainly intratumoral with a smaller peritumoral presence. More than 3 lymphocytes per high power field were noted within the tumour. The lymphocytes were small, round and mature appearing. The tumour extended into the superficial muscularis propria but there was no lympho-vascular invasion. All 13 sampled lymph nodes showed reactive change and the pathological stage was T2 NO LEL carcinoma with all resection margins being clear.

The tumour was positive for cytokeratin and EMA but negative for CK7, CK20, CDX-2, ER, PR, chromogranin, synaptophysin and EBV-LMP. Only occasional cells showed p53 positivity. With regards to the mismatch repair proteins, there was concordant MLH-1 and PMS-2 (Figure 4) loss with retention of both MSH-2 and MSH-
6. Occasional lymphocytes showed EBER-ISH positivity but the tumour cells were completely negative.

Discussion

LEL carcinomas in the GIT are mainly seen in the stomach and gastric carcinomas with a lymphoid stroma constitute about 4% of all gastric carcinomas [9,10]. Two subsets of gastric cancer, EBV-positive and microsatellite instability (MSI) high cancers have been associated with a lymphocyte-rich phenotype [11]. EBV is associated with 5-20% of gastric carcinomas worldwide [12-14], but more than 80% of LEL gastric carcinomas have been found to be related to EBV infection [2] compared to only about 6% to 7% of non-LEL (diffuse or intestinal) adenocarcinomas [15]. The reported prevalence of MSI-high in gastric carcinomas ranges from 7-39%, with apparent geographic variability accounting for such a wide range [2].

In LEL gastric carcinomas, the tumour cells are characteristically arranged in micro-alveolar, thin trabecular, and primitive tubular patterns, as demonstrated in our colonic case [16-18]. The tumour cells are large, oval or polygonal in shape, contain vesicular to clear nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm with poorly defined cell borders [19,20]. Invariably, there are more infiltrating lymphocytes than tumour cells [21]. The small lymphocytes can also infiltrate into cancer cell nests and epithelioid granulomas are sometimes observed within the lymphoid stroma [21]. The lymphoid reaction is composed predominantly of T-cells including numerous TIA-1 positive activated cytotoxic lymphocytes and/or natural killer cells in close contact with tumour cells [22]. The mechanism for the abundant lymphocytic infiltrate in LEL carcinomas remains unclear. The lymphoid reaction could be a direct response either to the virus or to virally-induced antigens expressed on the neoplastic cells [23]. Several authors have documented the strong association of EBV with LEL gastric carcinomas and this is thought to be the main reason for the lymphocytic response [24]. In cases not associated with EBV but with a MSI-high profile, some have proposed that the inflammatory infiltrate represents an effective host response against the tumour cells [11,15].

An etiologic association between EBV and gastric carcinomas is based on the uniform expression in all tumour cells of EBV and its absence in normal epithelium or dysplastic lesions [25]. The mechanism by which EBV contributes to the carcinogenesis in gastric mucosa is still unknown [26,27]. Interestingly, EBV is not expressed or detected in the lymphoid cells either, EBV-associated gastric carcinoma with lymphoid stroma has been confirmed to be composed of a monoclonal proliferation of a single EBV-infected progenitor cell, occurring before neoplastic transformation and is thus involved in the early stage of gastric carcinogenesis [28-30].

With regards to colonic LEL carcinomas, thus far only 5 other cases have been reported [4-8]. Vilor and Tsutsumi first documented LEL carcinoma of the colon in 1995 [4]. The patient was a 77-year old female with a transverse colon mass which was EBV-negative. The case described by Samaha et al occurred in the caecum of a 62-year old man and was EBV-positive by PCR [5]. The case of De Petris et al was a 44-year old male who had HNPCC but was EBER-ISH negative although a weak signal for EBV was obtained by PCR [6]. A rectal LEL carcinoma described by Kon et al was EBV positive [7]. The most recent case was a sigmoid colon tumour in a 25-year male with ulcerative colitis [8]. This case had weak EBER-ISH positivity in tumour cells. In the case under discussion, strong EBER-ISH staining was seen in occasional surrounding lymphocytes but not in the tumour cells. In the cases in which PCR amplification of EBV was detected [5,6], it should be borne in mind that then positivity may in fact be due to EBV-positive lymphoid cells rather than tumour cells containing EBV. Kojima et al obtained weak EBER-ISH positivity in tumour cells [8]. However, Kon and colleagues demonstrated EBNA-2 immunoreactivity and EBER-ISH positivity in occasional tumour cells in their case suggesting that is the only bona fide example thus far of an EBV-positive LEL in the colorectum [7].

In our case, the cancer cells showed loss of expression for both MLH-1 and PMS-2 thereby making this LEL carcinoma MSI-high [11]. The patient did not have a family history of colon cancer and did not fulfil any of the Amsterdam criteria for HNPCC. We feel that this is a sporadic epigenetic hypermethylation of MLH-1 and its partner dimer, PMS-2 leading to a MSI-high
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Colon cancer which has attracted the dense lymphocytic population and the LEL carcinoma phenotype.

LEL-carcinoma must be separated from medullary carcinoma of colon, which can also be encountered in HNPCC and causes confusion because it too is associated with a dense lymphoid infiltrate. Medullary carcinoma of the colon has a resemblance to high-grade neuroendocrine carcinoma in that it is packeted, in cords or sheets, contain areas of geographic necrosis and may demonstrate neuro-endocrine differentiation (up to 20% of cases). The vast majority (90%) show peritumoral and intratumoral lymphocytes at least focally [31]. In medullary carcinoma there are more peritumoral than intratumoral lymphocytes, it has a pushing rather than infiltrative margin and the tumour cells are uniform rather than pleomorphic as seen in LEL carcinoma.

We describe an unusual EBV-negative but sporadic MSI-high case of LEL carcinoma in the colon, which has all the histologic hallmarks of EBV-positive cases. It would appear that LEL carcinomas in the GIT outside of the stomach are different in that they do not have the strong association with EBV like gastric cases, and may in fact be more strongly associated with MSI.

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References


Figure 4. MLH-1 staining showing loss of nuclear positivity within the tumour while the surrounding lymphocytes retained the normal nuclear immunoreactivity.
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