Collision tumor of colonic adenocarcinoma and EBV-driven large B-cell lymphoma: A case report and review of literature

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Abstract

Introduction: Collision tumors of adenocarcinoma and lymphoma in the gastrointestinal tract are especially rare with few reported cases in literature. We report a unique case of a collision tumor and perform a literature review. Presentation of case: An 86-year-old patient with a history of rheumatoid arthritis on chronic azathioprine and prednisone was found to have an invasive adenocarcinoma in the descending colon. A large atypical lymphocytic infiltrate was found at the base of this lesion, which demonstrated CD20, lambda and EBER positivity consistent with adenocarcinoma colliding with EBV-driven and lambda-restricted large B-cell lymphoma. Discussion: With this report, there are now fifteen cases of this type of collision tumor although the true incidence may be higher. Our case is unique among previous reports as the collision developed within the setting of iatrogenic immunosuppression and tumor EBV positivity was demonstrated. The pathogenesis is unknown, and diagnosis requires a high-degree of suspicion. Conclusion: It is important to consider immunosuppression in a patient with adenocarcinoma, as presence of atypical lymphoid cells may be indicative of lymphoma.

1. Introduction

Colorectal adenocarcinoma is one of the most common neoplasms worldwide with more than half occurring in developed regions [1]. In contrast, primary gastrointestinal lymphoma is much more uncommon and defined by extranodal origin, normal white blood cell count, and lack of involvement of peripheral or mediastinal lymph nodes, liver, and spleen [2]. The vast majority are found in the stomach, while prior studies in the United States showed from 8.5 to 10% arising from the large intestine [3-5]. Although rare, the occurrence of primary colorectal adenocarcinoma with primary lymphoma has been previously well-documented in literature, [6] with the probability of synchronous...
occurrence estimated to be 2% [7]. Furthermore, synchronous multiple primary tumors that are histologically distinct and occur adjacently are even more rare [8]. These are defined as collision tumors. To date, only fourteen cases of collisions of colorectal adenocarcinoma and colonic lymphoma have been previously reported. We describe the clinicopathologic features of a patient with adenocarcinoma of the colon colliding with EBV-driven large B-cell lymphoma in the setting of chronic immunosuppression. A review of literature is also performed.

2. Case report

An 86 year-old female presented with bloody diarrhea, abdominal pain, and anemia. Past medical history was significant for rheumatoid arthritis treated with prednisone and azathioprine. Physical exam was unremarkable and no lymphadenopathy or organomegaly was noted. Laboratory studies revealed white blood count 3500/µL and hemoglobin 8.6 g/dL. Colonoscopy showed mass lesions at the cecum and splenic flexure, and biopsies showed adenocarcinoma.

Figure 1  Gross examination: (A) a 6.6 × 3.2 cm² soft, tan, exophytic mass with focal mucosal ulceration at the cecum and (B) a 6.5 × 4.5 cm² ulcerated lesion in the descending colon with heaped-up margins and necrotic appearing central area. Histologic examination (C-F): cecal tubulovillous adenoma with atypical lymphocytic infiltrates at the base with increased mitotic activity (C, × 100; E, × 400); low grade adenocarcinoma with a focus of high grade adenocarcinoma admixed with atypical lymphocytic infiltrates in the descending colon (D, × 100; F, × 400) (arrowheads indicate mitotic figures).
The patient underwent right extended hemicolectomy to the splenic flexure. Gross examination revealed a surgical specimen measuring 35 cm with a 6.6 × 3.2 cm² soft, tan, exophytic mass with focal mucosal ulceration at the cecum (Figure 1A) grossly invading the bowel wall and a 6.5 × 4.5 cm² ulcerated lesion in the descending colon (Figure 1B) with heaped-up margins and necrotic appearing central area that was grossly invading the subserosal fat. The terminal ileum and appendix were unremarkable.

Histologic examination of the cecal mass showed tubulo-villous adenoma (Figure 1C and E) with foci of high grade dysplasia/adenocarcinoma in situ, while the descending colon mass showed low grade adenocarcinoma with a focus of high grade component (Figure 1D and F) invading through the muscularis propria. Extensive moderate-to-large atypical lymphocytic infiltrates with increased mitotic activity were noted at the base of both lesions (Figure 1C and F). Immunohistochemistry of the lymphocytic infiltrates at both sites were strongly and diffusely positive for CD20, positive for lambda, and negative for kappa, while CD3 highlighted some background mature T-cells (Figure 2A-C). EBV encoding region in situ hybridization (EBER ISH) in the atypical B-cells was positive (Figure 2D). Expression of DNA mismatch repair proteins in the descending colon mass was found to be intact.

The patient was discharged twelve days after resection. No chemotherapy was initiated and the patient was instructed to discontinue prednisone and azathioprine. No recurrence was noted six months after the procedure.

3. Discussion

The pathogenesis of collision tumors has not been well-established. Given the synchronous presentation, it is difficult to determine the temporal or causal relationship, if any, between two primaries. Multiple primary tumors may arise from a single factor including: environmental, genetic, or immune system dysfunction [7]. A primary tumor may cause cytokine dysregulation or decreased immune surveillance to allow localized development of another primary. In contrast, given the rarity of occurrence, it is possible that collision tumors are merely an accidental event. Collision tumors in the gastrointestinal tract are especially rare; however, the number could be under reported. First, definitions may vary, with some reports not categorizing it as such. Second, in our literature review, we were unable to verify reports in non-English literature. Lastly, collision tumors are often difficult to diagnose given the nonspecific symptoms, and the presence of lymphoproliferative cells on histology is often thought to be reactive changes.

To our knowledge, there are fifteen cases of this type of collision to date, including this report (Table 1) [9-22]. There is a male and elderly predominance at an average age...
<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Age/sex</th>
<th>Signs and symptoms</th>
<th>Tumor location</th>
<th>Lymphoma type</th>
<th>Immuno-suppression</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornes et al. [9]</td>
<td>1960</td>
<td>63/M</td>
<td>Tenesmus, rectal bleeding, weight loss</td>
<td>Rectum</td>
<td>Lymphocytic lymphosarcoma</td>
<td>NA</td>
<td>Resection</td>
<td>1 year after resection: died of uremia secondary to urinary obstruction and enlarged prostate</td>
</tr>
<tr>
<td>Aitani et al. [10]</td>
<td>1987</td>
<td>59/M</td>
<td>NA</td>
<td>Transverse</td>
<td>Diffuse large B-cell</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mannweiler et al. [12]</td>
<td>2003</td>
<td>73/M</td>
<td>Diarrhea, abdominal pain</td>
<td>Rectum</td>
<td>Peripheral T-cell</td>
<td>NA</td>
<td>Resection</td>
<td>NA</td>
</tr>
<tr>
<td>Padmanabhan et al. [13]</td>
<td>2003</td>
<td>85/M</td>
<td>Blood per rectum, dizziness</td>
<td>Cecum</td>
<td>Mantle cell</td>
<td>NA</td>
<td>Resection</td>
<td>1 month after resection: died of ruptured abdominal aneurysm and myocardial infarction</td>
</tr>
<tr>
<td>Minato et al. [14]</td>
<td>2004</td>
<td>80/M</td>
<td>Right lower quadrant pain, anemia</td>
<td>Ascending</td>
<td>Diffuse large B-cell</td>
<td>NA</td>
<td>NA</td>
<td>5 months after diagnosis: died of MRSA pneumonia</td>
</tr>
<tr>
<td>Eshra et al. [15]</td>
<td>2010</td>
<td>67/M</td>
<td>Intestinal obstruction</td>
<td>Ascending</td>
<td>Marginal zone</td>
<td>NA</td>
<td>Resection</td>
<td>After resection: transferred to another institution for further adjuvant therapy</td>
</tr>
<tr>
<td>Sasaki et al. [16]</td>
<td>2010</td>
<td>62/M</td>
<td>Right lower quadrant pain, anemia</td>
<td>Cecum</td>
<td>Follicular</td>
<td>NA</td>
<td>Resection with six cycles of CHOP + Rituximab for lymphoma involving the duodenum</td>
<td>After initial chemotherapy: began mFOLFOX6 for metastatic adenocarcinoma to liver</td>
</tr>
<tr>
<td>Tokoro et al. [17]</td>
<td>2010</td>
<td>70/M</td>
<td>Anemia, weight loss, fecal occult blood</td>
<td>Rectum</td>
<td>Diffuse large B-cell</td>
<td>NA</td>
<td>Resection</td>
<td>23 days after resection and second reconstruction: died of aspiration pneumonia</td>
</tr>
<tr>
<td>Chang et al. [18]</td>
<td>2011</td>
<td>86/M</td>
<td>Tinnitus, visual acuity impairment</td>
<td>Cecum</td>
<td>Diffuse large B-cell</td>
<td>NA</td>
<td>Rituximab, cyclophosphamide, vincristine, prednisone for three cycles of 21 days, followed by resection, followed by monthly vincristine and prednisolone</td>
<td>16 months after initial presentation: found to have hepatic tumor but no intervention performed</td>
</tr>
<tr>
<td>Devi et al. [19]</td>
<td>2011</td>
<td>68/F</td>
<td>Bleeding per rectum</td>
<td>Ascending</td>
<td>MALT</td>
<td>NA</td>
<td>Resection</td>
<td>2 months after resection: no recurrence noted</td>
</tr>
<tr>
<td>Shigeno et al. [20]</td>
<td>2011</td>
<td>76/F</td>
<td>Ileocecal</td>
<td>Ileocecal</td>
<td>Diffuse large B-cell</td>
<td>NA</td>
<td>Resection</td>
<td></td>
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</table>
The majority of collisions arise in the cecum or rectum, with eight arising from the right colon, one from the transverse colon, and six from the left colon. The most common lymphoma found was diffuse large B-cell lymphoma. Of note, most cases initially presented with signs and symptoms suggestive of gastrointestinal disease and were subsequently found to have lymphoma, except for those described by Chang et al. [18] and Lin et al. [21].

In our case, the patient was found to have low grade adenocarcinoma in the descending colon and tubulovillous adenoma in the cecum both colliding with EBV-driven, lambda-restricted large B-cell lymphoma. Analysis of DNA mismatch repair proteins showed that a genetic or epigenetic cause of the collision tumor was not likely. Two other unique findings in this present case were not reported in our review of previous cases. First, the patient developed a collision tumor in the setting of iatrogenic immunodeficiency from chronic prednisone and azathioprine use. Second, EBV positivity was demonstrated in tumor. Given these findings, the development of large B-cell lymphoma in this patient was determined to be driven by EBV, with immunosuppression being the underlying cause.

We propose that immune dysregulation is the inciting factor in collision tumors of the gastrointestinal tract. This can be seen in the increased risk of lymphoma in patients with inflammatory bowel disease on immunosuppression [23-25]. The incidence of post-transplant lymphoproliferative disorders has been shown to increase with EBV viral load [26]. EBV has also been detected in colorectal adenocarcinoma, suggesting it as a possible contributing factor [27-28]. In our case, we postulate that iatrogenic immunosuppression allowed for proliferation of EBV, resulting in a microenvironment susceptible to development of lymphoma and subsequently adenocarcinoma. The presence of the tubulovillous adenoma with underlying EBV positive large B-cell lymphoma supports this mechanism, as it represents an earlier stage in the adenoma-to-carcinoma sequence.

Given the rarity of occurrence, optimal treatment of these collision tumors is unknown. Since collision tumors are adjacent, it is likely that the initial management would parallel the management of colorectal cancer. In the majority of cases, the treatment approach involved resection and a primary lymphoma was subsequently identified on histologic examination. In contrast, there were four cases in which chemotherapy was part of the management. Two of these four cases included chemotherapy because subsequent work-up following resection revealed lymphoma in another location. Thus, further diagnostic studies may be warranted with the finding of a collision tumor.

4. Conclusion

Collision tumors of colorectal adenocarcinoma and lymphoma are rare, although the true incidence may be higher than reported. The pathogenesis of collision tumors is difficult to elucidate given the uncommon occurrence. Diagnosis requires a high-degree of suspicion as it may be difficult to distinguish primary lymphoma from benign reactive changes. It is important to consider immunosuppression in a patient with adenocarcinoma, as a mixed
pattern or atypical lymphoid cells may be indicative of lymphoma.

References


