Rapid progression of colonic mucinous adenocarcinoma with immunosuppressive condition: A case report and review of literature

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Abstract

BACKGROUND
Colorectal mucinous adenocarcinoma is a rare subtype of colorectal cancer and is characterized by an abundance of mucin in the tumor. In addition, the colorectal mucinous adenocarcinoma often demonstrates poor differentiation in the histology of tumor cells and poor prognosis compared with those with adenocarcinoma. Here, we present the case of a young woman with colonic mucinous adenocarcinoma showing significantly rapid progression within four months of immunosuppressant therapy for Henoch-Schönlein purpura.

CASE SUMMARY
Here we report a rare case of ascending colon mucinous adenocarcinoma with lymph node and liver metastases which developed and progressed rapidly within four months during the treatment of Henoch-Schönlein purpura using corticosteroids. The systemic screening examinations showed no tumors before the immunosuppressant therapy. Fortunately, the patient was successfully treated with chemotherapy.

CONCLUSION
While no direct evidence that the immunosuppressants accelerated the tumor development, the case presentation and review of the literature demonstrated that surveillance for malignancies before and during treatment with immunosuppressive agents is essential.
A 37-year-old woman was referred to our department in August 2019 due to an acute exacerbation of her symptoms. She had been diagnosed with Henoch–Schönlein purpura (HSP) in 2017, which was followed by the development of gastrointestinal symptoms. She was treated with corticosteroids and immunosuppressive agents, but her condition deteriorated rapidly. The patient presented with neurological symptoms such as headache, dizziness, and focal numbness in the right upper and lower extremities. A CT scan performed in March 2019 revealed no gross lesions or malignancies. After four months of prednisolone (PSL) administration, the neurological symptoms improved; however, the levels of hepatobiliary enzymes increased significantly.

The patient was diagnosed with colorectal mucinous adenocarcinoma at stage IV, which had progressed rapidly within four months of treatment with corticosteroids. The disease was successfully treated with chemotherapy. Although there was no direct evidence that the immunosuppressants accelerated the tumor development, the case presentation and review of the relevant literature highlights the importance of surveillance for malignancies before and during treatment with immunosuppressive agents.

INTRODUCTION

Colorectal mucinous adenocarcinoma is a subtype of colorectal cancer that accounts for approximately 10% of colorectal cancers and is characterized by an abundance of mucin in the tumor. It is often diagnosed in young women and in the right-sided colon at an advanced stage. Patients with colorectal mucinous adenocarcinoma often demonstrate rapid progression and poor differentiation in the histology of tumor cells compared with those with adenocarcinoma. Here, we present the case of a young woman with ascending colon mucinous adenocarcinoma diagnosed at stage IV, which developed and progressed rapidly within four months during the treatment of Henoch–Schönlein purpura using corticosteroids. The patient was successfully treated with chemotherapy. Although there was no direct evidence that the immunosuppressants accelerated the tumor development, the case presentation and review of the literature demonstrated that surveillance for malignancies before and during treatment with immunosuppressive agents is essential.

CASE PRESENTATION

Chief complaints
A 37-year-old woman was referred to our department in August 2019 due to an increase in the levels of hepatobiliary enzymes.

History of present illness
After four months of prednisolone (PSL) administration, the neurological symptoms improved; however, the levels of hepatobiliary enzymes, which were normal before the pulse therapy, increased. Contrast-enhanced computed tomography (CT) performed in March 2019 as a screening examination to detect potential infectious lesions or malignancies before the pulse therapy showed no gross lesions in the gastrointestinal tract, lungs, liver, gall bladder, pancreas, spleen, kidneys, and adrenal glands and no swelling in the lymph nodes.

History of past illness
She had no familial history of cancer but had a history of Henoch–Schönlein purpura (HSP) diagnosed in 2017 via a renal biopsy and was treated with corticosteroids starting at 30 mg/d oral PSL, which was tapered down to 1 mg till February 2019. In March 2019, she presented with neurological symptoms of headache, dizziness, and focal numbness in the right upper and lower extremities, with no evidence of infarction or bleeding in clinical and imaging tests.
of the purpura with neurological symptoms and was treated with methylprednisolone pulse therapy, followed by continuation of oral PSL administration.

**Personal and family history**
She had no personal and family history of the malignancies.

**Physical examination**
Other than the palpable abdominal masses in the epigastric lesion with mild tenderness and a symmetric pitting edema in her lower legs, no abnormal findings in her vital signs and other physical examination were noted.

**Laboratory examinations**
The results of a laboratory test performed on the day of admission revealed elevated white blood cell counts and levels of aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and γ-glutamyl transpeptidase (Table 2). During the four-month period after re-dosing of PSL in March 2019, the levels of the tumor markers...
Table 2 Laboratory on admission

|                  | Hematology | Biochemistry | Marker |
|------------------|------------|--------------|--------|
|                  | Values     | Normal range | Values | Normal range | Values | Normal range |
| WBC              | 12850      | 3300-8600/µL | TP     | 6.3         | 6.6-8.1 g/dL | CEA    | 97.0         | < 5.8 ng/mL |
| Neutro.          | 93.7       | 38.0%-71.0%  | Alb    | 3.6         | 4.1-5.1 g/dL | CA19-9 | 255          | < 37 IU/mL |
| Lymph.           | 4.7        | 21.0%-50.0%  | BUN    | 10          | 8-20 mg/dL  | AFP    | 1            | < 9.5 ng/mL |
| Eos.             | 0.0        | 7.3%         | Cre    | 0.76        | 0.46-0.79 mg/dL | AFP-L3 | < 0.5        | < 10 %     |
| Bas.             | 0.1        | 2.0%         | T-Bil  | 0.8         | 0.4-1.5 mg/dL | PIVKA-II | 22.0        | < 37.8 ng/mL |
| Mon.             | 1.5        | 3.0%-8.0%    | AST    | 107         | 13-30 IU/L  | IL-2R  | 1031         | 122-496 U/mL |
| RBC              | 395        | 386-492 ×10⁶/µL | ALT    | 165         | 7-23 IU/L   |        |              |              |
| Hb               | 11.0       | 11.6-14.8 g/dL | ALP    | 1156        | 106-322 IU/L |        |              |              |
| Ht.              | 35.2       | 35.1%-44.4%  | LDH    | 1309        | 124-222 IU/L |        |              |              |
| Plt.             | 36.6       | 15.8-34.8 ×10⁴/µL | γ-GTP | 489         | 9-32 IU/L   |        |              |              |
|                  |            |              | Na     | 136         | 138-145 mEq/L |        |              |              |
|                  |            |              | K      | 4.0         | 3.6-4.8 mEq/L |        |              |              |
|                  |            |              | Cl     | 99          | 101-108 mEq/L |        |              |              |
|                  |            |              | Ca     | 9.1         | 8.8-10.1 mg/dL |        |              |              |
|                  |            |              | CRP    | 1.96        | < 0.14 mg/dL |        |              |              |

WBC: White blood cell; Neutro.: Neutrophil; Lymph.: Lymphocyte; Eos.: Eosinophil; Bas.: Basophil; Mon.: Monocyte; RBC: Red blood cell; Hb: Hemoglobin; Ht.: Hematocrit; Plt.: Platelets; PT%: Prothrombin time; PT-INR: Prothrombin time-international normalized ratio; APTT: Activated partial thromboplastin time; TP: Total protein; Alb: albumin; BUN: blood urea nitrogen; Cre: Creatinine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; γ-GTP: γ-glutamyl transpeptidase; ChE: Cholinesterase; Na: sodium; K: Potassium; Cl: Chloride; P: Phosphate; Ca: Calcium; CRP: C-reactive protein.

carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 significantly increased from 1.1 ng/mL to 97.0 ng/mL and 14 IU/mL to 255 IU/mL, respectively. To investigate the cause of the elevation in liver enzyme levels, further examinations were conducted.

**Imaging examinations**

Contrast-enhanced CT revealed a suspicious tumor in the ascending colon with an irregularly thickened intestinal wall and swelling in multiple lymph nodes (six regional lymph nodes) surrounding the ascending colon tumor. In addition, multiple low-density liver tumors showing poor enhancement effect with expanding growth pattern were observed, and the intrahepatic bile duct exhibited mild dilatation due to the tumors (Figure 1C and D). No other suspicious lesions for the primary were seen. Abdominal ultrasonography revealed multiple tumors in the bilateral liver lobes up to 80 mm in size with heterogeneously high echoic patterns (Figure 2A and B). Colonoscopy revealed a large, solid, multinodular epithelial tumor in the ascending colon. The tumor was on the epithelial layer and covered with whitish mucus and debris on its surface with an abnormal vascular structure on its surface and was easily bleeding (Figure 2C). In addition, the tumor showed a semicircular depressive lesion at its center (Figure 2D and E). The histological analyses of the tissue collected from the tumor (black arrow shown in Figure 2C) revealed an abundant amount of extracellular mucin within the tumor on the mucosal epithelia. The tumor cells in the mucin appeared to be adenocarcinoma cells showing a high level of cellular atypia and tended to resemble cells of the glandular tissue (Figure 3A and B). The tumor cells positively stained for Mucin 2, oligomeric mucus/gel-forming (Figure 3C) and Mucin 5AC (Figure 3D). Based on these CT, endoscopic, and histological analyses, the case was diagnosed with the ascending colon mucinous adenocarcinoma.
Table 3 Summary of colorectal cancer after organ transplantation

| No. | Ref. | Immunosuppressant | No. of cases | CRC (occurrence rate, %) | Yr to diagnosis (median, range) | Lesion | Proximal colon (%) | Distal colon (%) | Rectum (%) | UD (%) | SIR | 95%CI |
|-----|------|-------------------|--------------|--------------------------|-------------------------------|--------|---------------------|----------------|-------------|---------|------|------|
| 1   | Safaeian et al [20] | AZA, CsA, MMF, TAC | 224098      | 790 (0.3)                | N/A                           | 408 (51.6) | 195 (24.7) | 146 (18.5) | 41 (5.2) | 1.12 | 1.04-1.20 |
| 2   | Huo et al [21] | N/A               | 2105122     | 53 (0.003)               | N/A                           | N/A     | N/A     | N/A     | N/A | 1.82 | 1.59-2.09 |
| 3   | Engels et al [22] | N/A               | 173732      | 627 (0.4)                | N/A                           | N/A     | N/A     | N/A     | N/A | 1.24 | 1.15-1.34 |
| 4   | Buell et al [23] | AZA, CsA, MMF, TAC | 13000       | 141 (1.1)                | N/A                           | N/A     | N/A     | N/A     | N/A | 1.94 | 1.64-2.59 |
| 5   | Aberg et al [24] | CsA, TAC, antibody | 540         | 2 (0.4)                  | N/A                           | N/A     | N/A     | N/A     | N/A | 1.59 | 0.19-5.74 |
| 6   | Merchea et al [26] | AZA, CsA, MMF, TAC, steroid | 3946      | 20 (0.5)                 | 8.7 (0.4-19)                  | 14 (70) | 4 (20) | 2 (10) | 0 (0) | N/A | N/A |
| 7   | Rompianesi et al [27] | N/A               | 8178        | 34 (0.4)                 | 5.6 (3.8-8.8)                 | 17 (50) | 9 (26.5) | 8 (23.5) | 0 (0) | 0.92 | 0.69-1.20 |
| 8   | Aigner et al [28] | AZA, CsA, MMF, TAC, steroid | 3595      | 9 (0.3)                  | 5.3 (1.5-10)                 | 4 | 1 | 4 | 0 (0) | N/A | N/A |
| 9   | Rademacher et al [29] | AZA, CsA, MMF, TAC, steroid | 1616      | 22 (1.3)                 | 8.2 (0.3-19.9)               | N/A | N/A | N/A | N/A | 1.9 | 1.2-2.9 |
| 10  | Haagsma et al [30] | N/A               | 174         | 3 (1.7)                  | 7.9 (5.9-16.7)               | N/A | N/A | N/A | N/A | N/A | N/A |
| 11  | Park et al [31] | CsA, TAC, Sirolimus, AZA, MMF | 360         | 4 (1.1)                  | N/A                           | N/A | N/A | N/A | N/A | N/A | N/A |

AZA: Azathioprine; CsA: Cyclosporine; MMF: Mycophenolate mofetil; TAC: Tacrolimus; CRC: Colorectal cancer; UD: Undetermined; SIR: Standardized incidence ratio; N/A, data not available.

**FINAL DIAGNOSIS**

Based on this information, the tumor was diagnosed as mucinous adenocarcinoma. Overall, the patient was diagnosed with ascending mucinous colorectal adenocarcinoma with lymph node and liver metastases, and based on the Tumor, Node, Metastasis staging system from the American Joint Committee on Cancer (8th edition), the clinical stage was determined as cT4aN2aM1a.

**TREATMENT**

Chemotherapy was started with the combination of fluorouracil, oxaliplatin, and leovofolinate (mFOLFOX6; four courses), followed by the combination of irinotecan and mFOLFOX6 (FOLFIRINOX; two courses), after normalization of the levels of hepatobiliary enzymes, which could be due to the shrinkage of the metastatic liver tumors (Figure 4A).

**OUTCOME AND FOLLOW-UP**

CT was performed on day 180, after chemotherapy treatment resulted in the shrinkage of the primary colon tumor, lymph node, and liver metastasis (Figure 4B), and chemotherapy was continued. In addition, our case is under the investigation of microsatellite instability and endoscopic follow up will be conducted to screen the tumor progression.
DISCUSSION

Colorectal mucinous adenocarcinoma is a subtype of colorectal cancer characterized by an abundance of mucus, which accounts for at least 50% of the tumor volume[1]. Statistically, mucinous histological subtypes account for 10%–20% of colorectal cancers [2,3], whereas the rate is lower in Asian countries (4%–5%) [1,4-6]. Colorectal mucinous adenocarcinoma occurs more generally in young women and is more frequently located in the right colon and diagnosed at an advanced stage[1,4-6]. Moreover, colorectal mucinous adenocarcinoma often demonstrates rapid progression and lower curable resection rates compared with colorectal adenocarcinoma[4,5,7-13]. Furthermore, patients with colorectal mucinous adenocarcinoma often show poorer differentiation in the histology of the tumor cells and higher CEA levels than those with adenocarcinoma[4,13-15]. The case presented here was of a young woman with ascending colon mucinous adenocarcinoma diagnosed at stage IV, which developed and progressed rapidly, with an increase in the CEA level within 4 months, which is consistent with the characteristics reported previously[1,4-6,16]. The histological analyses of the tumor cells showed positively stained for Mucin 2 and Mucin 5AC which were reported to be significantly related to the colorectal mucinous adenocarcinoma[17,18]. The overall survival of patients with mucinous adenocarcinoma of the colon tends to be poorer than that of patients with non-mucinous carcinoma of the colon. The prognosis of patients with colorectal mucinous adenocarcinoma was similar to that of patients with non-mucinous carcinoma at stages I and II, whereas the prognosis was significantly poorer at stages III and IV[4]. One of the factors contributing to this poor prognosis is poor response to oxaliplatin, irinotecan, and fluorouracil-based first-line combination chemotherapy. While, fortunately, our patient showed a favorable response to the mFOLFOX6 and FOLFILINOX regimen, as previously reported, colorectal mucinous adenocarcinoma has a higher rate of microsatellite instability than non-mucinous colorectal adenocarcinoma[1,13,19], and the administration of immune checkpoint inhibitors might be useful for these types of cells, our case is under the investigation of microsatellite instability.

In this case, it is noteworthy that rapid progression was observed during the period of significant increase of immunosuppressant medication due to the recurrence of the HSP. Although colonoscopy was not performed before the administration of PSL and the initial missing possibility can’t be excluded, CT revealed no tumor in the colon or in other organs. During these four months, tumor development was seen in the colon.

Figure 1 Computed tomography before corticosteroid administration and four months after the therapy. A and B: No significant findings were noted before corticosteroid administration; C: Tumorous lesion in the ascending colon (white arrowheads) and suspicion of lymph node metastasis (orange arrowheads) were noted; D: A significant number of low-density masses in the liver up to 80 mm in size (orange arrows) were confirmed. Mild dilatation of the intrahepatic bile duct was noted (black arrow).
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Figure 2 Ultrasonographic and endoscopic images of the tumor. A and B: Abdominal ultrasonography revealed multiple iso- to high-echoic masses in bilateral liver lobes (white arrows). C-E: Endoscopic findings of the colon tumor. A large, solid, multinodular tumor on the epithelial layer (black arrow) with a semicircular depressive lesion at its center in the surface (black arrowheads) was observed in the ascending colon. The tumor was covered with whitish mucus and debris (white arrowheads), with an abnormal vascular structure on its surface (white arrows). Along with severe metastatic lesions in the liver and lymph nodes. Long-term use of immunosuppressants has been associated with an increased incidence of various cancers[20-27] and glucocorticoid therapy has been reported to transduce the signal for tumor progression[26]. Among cancers, colorectal cancer is rare, occurring in 0.003%-1.7% of cases treated with immunosuppressant therapy during the study period (Table 3)[20-24,26-31]. Table 3 summarizes the cases of patients who developed colorectal cancer during the period of treatment with immunosuppressants. They received a combination of either an antimetabolite (mycophenolate mofetil or azathioprine) or a calcineurin inhibitor (tacrolimus or cyclosporine) in addition to PSL. The median time from transplantation to diagnosis of colon cancer is 5.3-8.7 years, and tumors were most commonly found in the proximal side colon, including the ascending and transverse colons (Table 3), which was also the primary site in our case. As our case showed rapid progression within four months, it is possible that atypia of the cells with poor differentiation along with immunosuppression affected the growth of tumor cells. The higher risk of the colorectal neoplasia[31] and advanced colonic adenomatous polyps[32] were further reported in the solid organ transplantation recipients under the immunosuppression, it is clear that the earlier surveillance has
Figure 3 Histological findings of the tumor. A and B: Hematoxylin and eosin staining. Mucus in the tumor (orange arrows) and adenocarcinoma cells in the mucus (black arrows). Black arrowhead shows the surface of the tumor and white arrowhead shows the bottom of the tumor; C: Mucin 2, oligomeric mucus gel-forming staining (orange arrows and white arrowheads represent positively stained mucosal cells and adenocarcinoma cells); D: Mucin 5AC staining (black arrowheads represent positively stained adenocarcinoma cells).

Figure 4 Ultrasonographic and endoscopic images of the tumor. A: Clinical course of the case; B: Computed tomography results on day 180. CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; PSL: Prednisolone; mFOLFOX6: Modified combination of 5-fluorouracil, leucovorin, and oxaliplatin; FOLFIRINOX: Combination of leucovorin, fluorouracil, irinotecan, and oxaliplatin. It has been recommended for these cases.
CONCLUSION

In summary, we report a rare case of ascending mucinous colorectal adenocarcinoma with lymphatic and liver metastases that developed within four months of immunosuppressant therapy. While no direct evidence was found that corticosteroid administration accelerated tumor development, it is clear that surveillance for malignancies before the induction of immunosuppressive agents is essential and that continuous and careful screening is essential, especially for cases treated with high-dose long-term immunosuppressants.

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