

Synchronous adenocarcinoma and extranodal natural killer/T-cell lymphoma of the colon: A case report and literature review

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Abstract

Extranodal natural killer/T-cell lymphoma (ENKTL) is a distinct subtype of non-Hodgkin's lymphoma and is rare in the colon. Synchronous adenocarcinoma and ENKTL of the colon has not been reported in the literature. In the present study, we report a 63-year-old male who suffered from intermittent bloody stools for 2 mo. He did not have fever, body weight loss or night sweat. Endoscopic and imaging studies revealed a 4.5-cm ulcerative mass in the ascending colon and a 3.0-cm polypoid, easy bleeding mass in the sigmoid colon, respectively. Thought to have double carcinoma of the colon, he received simultaneous right hemicolectomy and sigmoidectomy. The pathological diagnosis was a synchronous ENKTL (ascending colon) and adenocarcinoma (sigmoid colon). The literature on synchronous adenocarcinoma and malignant lymphoma of the colon

was also reviewed.

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Key words: Synchronous cancers of the colon; Colonic adenocarcinoma; Colonic lymphoma; Extranodal natural killer/T-cell lymphoma; Epstein-Barr virus

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INTRODUCTION

Malignant lymphoma of the colorectum is uncommon with an incidence of less than 0.5% of all malignant large intestinal tumors^[1], and comprises 5.8% of all gastrointestinal lymphomas^[2]. Synchronous colonic adenocarcinoma and malignant lymphoma in the same patient is rare with an estimated incidence of around 0.0002%^[3]. Synchronous colonic adenocarcinoma and extranodal natural killer/T-cell lymphoma of the colon has not been reported. Herein, we present such a rare case and review the literature.

CASE REPORT

A 63-year-old male with a 2-year history of hypertension and gout under medical control visited our outpatient department on April 25, 2012. He complained of intermittent bloody stool passage in the previous 2 mo. There was no B symptoms (fever, night sweating, body weight loss greater than 10% in the past 6 mo) noted. Dark red blood in the upper rectum was noted during

digital examination and tumor bleeding was suspected. Colonoscopy was performed one week later, which revealed an approximately 4-cm ulcerated mass coated with necrotic tissue in the proximal ascending colon near the ileocecal valve (Figure 1A). Another 3.5-cm bleeding mass was located 30 cm from the anal verge (Figure 1B). Biopsies were taken from the two masses, which showed necrotic tissue and adenocarcinoma *in situ*, respectively. After discussion, the patient was admitted for colectomy to remove the two masses. On admission, his vital signs and routine blood and biochemical studies were all within normal limits. The tumor marker, carcinoembryonic antigen, was mildly elevated at 9.4 ng/mL (normal range: 0-7 ng/mL). During preoperative evaluation, a computed tomography (CT) scan of the chest and abdomen was performed and revealed an irregular mass in the proximal ascending colon and a polypoid, protruding mass located in the sigmoid colon (Figure 1C). A tiny questionable pulmonary nodule (about 1-2 mm) of unknown nature in the left upper lung lobe was also noted at this time. Thought to have double carcinoma of the colon with sparing transverse and descending colon and for keeping well post-operative life quality, he underwent laparoscopic right hemicolectomy and sigmoidectomy with anastomosis on May 4, 2012. Grossly, the specimen from laparoscopic right hemicolectomy demonstrated an ulcerative mass, measuring 4.5 cm × 3.5 cm × 1.2 cm, in the proximal ascending colon with ileocecal valve involvement (Figure 1D). The tumor was yellow-green in color, ulcerative and necrotic. On cutting, the mass showed a yellowish fleshy cut surface and invaded serosa. Some enlarged lymph nodes, measuring up to 1.0 cm were noted. Microscopic examination revealed an ulcerative tumor composed of sheets of large pleomorphic lymphoid cells with a scattered angiocentric pattern and patchy necrosis (Figure 1E and F). The tumor had metastasized to three of the twelve right pericolic lymph nodes. On immunohistochemical study, the neoplastic lymphocytes were positively stained for CD3, CD56 (Figure 1G), T cell intracellular antigen 1 and CD30, but negatively stained for pancytokeratin, CD20, CD246 (ALK), CD4, CD8 and myeloperoxidase. An *in situ* hybridization (ISH) study revealed positive Epstein-Barr virus encoded RNA (EBER) in tumor nuclei (Figure 1H). Other parts of intestinal tissue showed no evidence of atrophic mucosa or enteropathy. The pathologic diagnosis was extranodal NK/T-cell lymphoma, nasal type, of the proximal ascending colon. The specimen from sigmoidectomy showed a red fleshy and polypoid mass, measuring 3.0 cm × 2.0 cm × 1.2 cm, taken from the central part of the sigmoid colon (Figure 1I). On cutting, the mass showed a polypoid, fleshy cut surface and invaded subserosa grossly. Microscopically, this tumor revealed marked pleomorphic tumor cells with complex glands, foci of cribriform formation, and an extensive infiltrative pattern (Figure 1J). The pathologic diagnosis was a moderately-differentiated adenocarcinoma. Four pericolic lymph nodes with no evidence of metastasis were retrieved in this specimen. An additional ISH

study of the adenocarcinoma showed negative EBER. In accordance with these findings, a synchronous adenocarcinoma of the sigmoid colon and extranodal natural killer/T-cell lymphoma (ENKTL) of the proximal ascending colon was finally diagnosed. His post-operative course was uneventful and he was discharged 10 d after surgery.

On June 14, 2012, the patient was readmitted for further tumor staging and chemotherapy. His ECOG performance score was grade 1. A tumor survey using sinuscopy showed no tumor in the upper respiratory tract. Bone marrow biopsy performed on June 16, 2012 revealed neither tumor nor granuloma. Biochemical studies showed a lactate dehydrogenase (LDH) level of 176 IU/L (normal range: 85-227 IU/L). A CT scan of the head, neck, chest and abdomen was performed and showed multiple nodules in bilateral lungs with the largest nodule being 1.2 cm in diameter in the left upper lung lobe. He then received chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). Unfortunately, a subsequent chest CT scan revealed rapid progression of bilateral lung nodules; the largest nodule being 5.4 cm in diameter in the right upper lung lobe on September 3, 2012 (Figure 1K). It was confirmed to be metastases of ENKTL by CT-guided biopsy (Figures 1L and M). In addition, serum LDH was markedly elevated at 1079 IU/L. Due to poor response to chemotherapy, the regimen was changed to dexamethasone, methotrexate, ifosfamide, *L*-asparaginase and etoposide but this was in vain. The patient died of respiratory failure secondary to lung metastasis on September 21, 2012. The survival time after diagnosis was only 4.5 mo.

DISCUSSION

The gastrointestinal tract is the most frequently involved extranodal site in non-Hodgkin lymphoma, stomach being the most common (50%-60%) followed by the small intestine (30%)^[4]. ENKTL is an extranodal lymphoma characterized by angioinvasion and damage, prominent necrosis, cytotoxic phenotype and associated with Epstein-Barr virus (EBV). Primary ENKTL of the gastrointestinal tract is very rare and carries a poor prognosis. The large intestine is the most common site in the gut affected by ENKTL followed by the small intestine^[5]. Synchronous adenocarcinoma and malignant lymphoma of the colon in the same patient is rare and only a few cases have been reported in the literature. Furthermore, synchronous colonic adenocarcinoma and ENKTL has never been reported.

The symptoms of colonic ENKTL are related to ulcerative plaques, or shallow multiple ulcerations, due to its angioinvasive nature, and may clinically manifest as abdominal pain and bloody stools, as seen in the present case. Due to its ulcerative nature in the colon, the differential diagnosis of ENKTL includes inflammatory bowel disease, tuberculous or cytomegaloviral infection, and neoplasm. There are no characteristic features to distin-

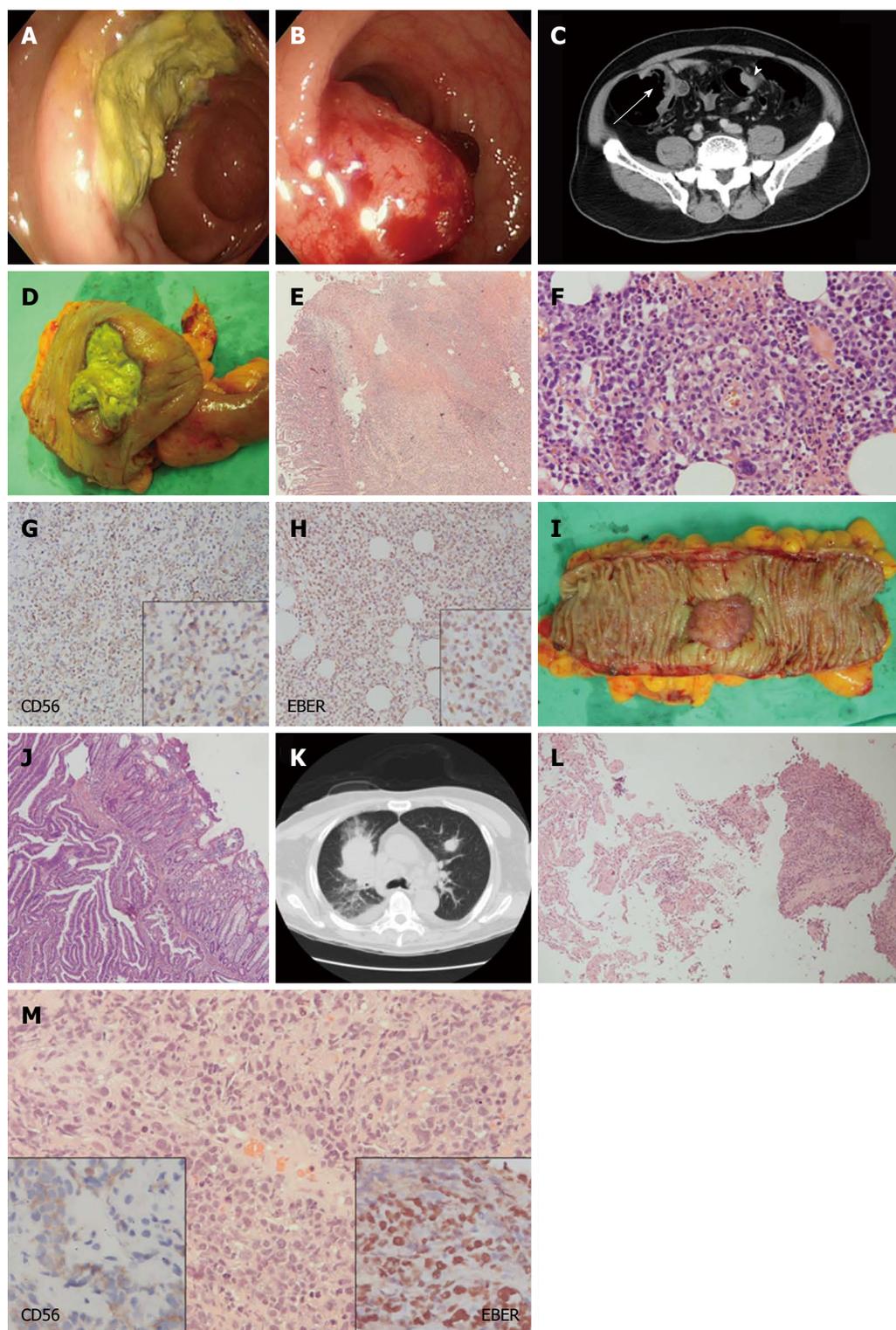


Figure 1 Clinical imaging studies and pathologic features of synchronous extranodal natural killer/T cell lymphoma and adenocarcinoma of the colon, as well as lung metastasis of the lymphoma. A: Appearance of the proximal ascending colon on colonoscopy: A marked ulcerative mass coated with necrotic tissue; B: Appearance of the sigmoid colon on colonoscopy: A polypoid bleeding mass; C: Computed tomography (CT) scan of the abdomen revealing a mass in the proximal ascending colon (arrow on the left) and another mass in the sigmoid colon (arrowhead on the right); D: Surgical specimen of the proximal ascending colon showing an ulcerative mass; E: Histologically, a section of the tumor from the proximal ascending colon showing neoplastic lymphoid cells (right lower part) infiltrating the colonic mucosa (left part) accompanied by a necrotic ulcer (upper middle part), hematoxylin and eosin (HE) stain, $\times 40$; F: Angioinvasion of the neoplastic lymphoid cells of the lymphoma, HE stain, $\times 400$; G: CD56 reactivity of the lymphoma cells, $\times 200$ (right lower inset, $\times 400$); H: Epstein-Barr virus encoded RNA (EBER) reactivity of the lymphoma cells, $\times 200$ (right lower inset, $\times 400$); I: Surgical specimen from the sigmoid colon revealing a polypoid, hemorrhagic mass; J: Histology of the sigmoid colon tumor showing adenocarcinoma with infiltrative neoplastic glands, HE stain, $\times 40$; K: Multiple lung metastases of the lymphoma on follow-up CT scan of the chest (the largest nodule on the right lung was biopsied); L: Histology of the lung biopsy showing lung parenchyma (on the left) and tumor cells (on the right), HE stain, $\times 100$; M: Histologically, a section of the lung biopsy showing the ovoid nucleated neoplastic cells with high N/C ratio, HE stain, $\times 400$, and reactivity of EBER (right lower inset, $\times 400$) and CD56 (left lower inset, $\times 400$).

Table 1 Synchronous adenocarcinoma and malignant lymphoma of colon in the literature

Year	Age/ gender	Tumor1/tumor2	Location1/location2	Pre-OP Dx	OP	Die of	Survival time (mo)
1984	14/M	Adenoca/large cell L	Rectosigmoid/cecum	Adenoca	R't hemicolectomy Sigmoidcolectomy	Sepsis	1
1985	52/F	Adenoca/ML	Ascending/ascending	Adenoca	R't hemicolectomy	ML	5
1995	74/F	Adenoca/MCL	Cecum, rectum/ileum, colon, rectum	Adenoca/MCL	Panproctectomy	-	-
1997	32/F	Adenoca/MALToma	Sigmoid/cecum	Double cancer	Subtotal colectomy	MALToma	17
2001	74/M	Adenoca/MCL	Rectum/sigmoid	Adenoca	LAR	-	4 mo alive
2001	54/M	Adenoca/MCL	Ascending/terminal ileum	Adenoca	R't hemicolectomy	-	6 mo alive
2003	85/M	Adenoca/MCL	Cecum/colon + terminal ileum	Adenoca	Ileocecal resection	Ruptured aneurysm	1
2009	80/M	Adenoca/MCL	Sigmoid/pericolic LN	Adenoca	Sigmoidectomy	MCL	14
2010	67/M	Adenoca + MALToma/FL	Ascending/terminal ileum	-	R't hemicolectomy	-	-
2011	86/M	Adenoca/SLL/CLL	R't colon/mesenteric LN	Adenoca	R't hemicolectomy	Loss F/U	-
2011	68/F	Adenoca/MALToma	Ascending/ascending	Adenoca	R't hemicolectomy	-	Alive
2012	79/F	Adenoca/AITL	Cecum/pericolic LN	Adenoca	R't hemicolectomy	-	-
2012 (the current case)	63/M	Adenoca/ENKTL	Ascending/sigmoid	Double cancer	R't hemicolectomy + sigmoidectomy	ENKTL lung metastasis	4.5

Adenoca: Adenocarcinoma; Large cell L: Large cell lymphoma; ML: Malignant lymphoma; MCL: Mantle cell lymphoma; MALToma: Mucosa-associated lymphoid tissue lymphoma; FL: Follicular lymphoma; SLL: Small cell lymphoma; CLL: Chronic lymphocytic leukemia; AITL: Angioimmunoblastic T-cell lymphoma; ENKTL: Extranodal natural killer/T-cell lymphoma; Rectosigmoid: Rectosigmoid colon; Ascending: Ascending colon; Sigmoid: Sigmoid colon; R't: Right; LAR: Low anterior resection; F/U: Follow-up.

guish colonic ENKTL from carcinoma from colofibrosopic and imaging viewpoints. This makes the preoperative diagnosis of colonic ENKTL challenging.

Synchronous colonic adenocarcinoma and malignant lymphoma is rare. There are only 13 reported cases, including the present case, in the literature (Table 1)^[6-16]. All these cases, with the exception of two (14-year-old and 32-year-old) were older than 50 years with a mean age of 63.7 years. Synchronous mantle cell lymphoma and adenocarcinoma (5 cases) were the most frequent diagnoses followed by synchronous extranodal marginal zone lymphoma of mucosa associated lymphoid tissue and adenocarcinoma (3 cases). The involved sections of the colon included the cecum, ascending colon, sigmoid colon and rectum. It is intriguing that the transverse colon and descending colon were spared in the reported cases including the present case. All cases except one of the synchronized colonic lymphoma were preoperatively diagnosed as colonic adenocarcinoma. This indicates that it is a challenge to preoperatively recognize synchronous colonic adenocarcinoma and malignant lymphoma. The most frequent surgical technique in these cases was right hemicolectomy (8 cases) since the right colon was the most common section involved. The overall survival time was relatively short with a mean of 7.6 mo (range: 1-17 mo). Four patients, including the present patient, out of the 13 cases died of lymphoma. In short, synchronous adenocarcinoma and malignant lymphoma of the colon involved aging patients, spared the transverse and descending colon and had a poor prognosis and short survival time.

The etiology of synchronous adenocarcinoma and malignant lymphoma of the colon is unknown. Chance coincidence is favored^[9,14]. However, local factors such

as absent immune surveillance in the lymphoma which possibly allowed carcinoma cells to grow has also been suggested^[8]. Recently, it was reported that EBV-derived latent membrane protein-1-induced protein may have an important role as a mediator in EBV-mediated neoplasms, including ENKTL^[17]. A low incidence of adenocarcinoma was also proven to be infected with EBV^[18]. Although EBV infection in adenocarcinoma of the sigmoid colon in our patient was not determined, the role of EBV in synchronous adenocarcinoma and ENKTL requires further elucidation.

In conclusion, synchronous adenocarcinoma and malignant lymphoma is uncommon. In particular, synchronous adenocarcinoma and ENKTL is extremely rare, with the present case being the only one reported, with poor prognosis. The etiology of this synchronization is still unknown. Chance coincidence or poor immunity in patients may contribute to the etiology, and the role of EBV needs further elucidation.

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