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CASE REPORT

Anaplastic lymphoma kinase-negative anaplastic large cell lymphoma masquerading as Behcet's disease: A case report and review of literature

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Abstract

BACKGROUND

Anaplastic large cell lymphoma (ALCL) is a CD30-positive T cell lymphoma, a rare type of non-Hodgkin lymphoma. The current World Health Organization classification system divides ALCLs into anaplastic lymphoma kinase (ALK)-positive and ALK-negative groups. ALCL rarely presents in the gastrointestinal tract.

CASE SUMMARY

A 54-year-old male was admitted to the department of gastroenterology for abdominal pain. He presented with lower abdominal pain, diarrhea and recurrent oral and penile ulcers. He was misdiagnosed with Behcet's disease and treated with prednisone. But after one month, he was hospitalized in another hospital for reexamination. This time, the lesion on the penis was biopsied for histological examination. The final pathological diagnosis was ALCL, ALK-negative. The patient was treated with cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy. However, he died within one month.

CONCLUSION

Gastrointestinal ALCL needs to be considered in the differential diagnosis to avoid delaying treatment. Repeated biopsy is the most important for early diagnosis and treatment.

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Core tip: Anaplastic large cell lymphoma (ALCL) is a CD30-positive T cell lymphoma, a rare kind of non-Hodgkin lymphomas. ALCL rarely presents with the intestinal tract. In addition to reporting an anaplastic lymphoma kinase-negative ALCL involving the colon and penis in a 54-year-old male, our literature review identified 3 cases of gastrointestinal ALCL with several interesting clinicopathological features.

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INTRODUCTION

Anaplastic large cell lymphoma (ALCL) is a peripheral T-cell lymphoma and is characterized by strong expression of CD30 (Ki-1)[1]. According to the World Health Organization (WHO) classification, ALCLs are divided into four groups: Systemic anaplastic lymphoma kinase (ALK)-positive ALCL (ALCL, ALK+), systemic ALK-negative ALCL (ALCL, ALK-), primary cutaneous ALCL (pC-ALCL), and breast implant-associated ALCL (BI-ALCL)[2]. Both ALK-positive and ALK-negative patients are predominantly male[1]. Two groups involve both lymph nodes and extranodal sites, and 20% of ALCL and ALK- patients have involvement of both sites[3]. In patients with ALCL, the ALK+ subtypes are more often seen in the first three decades of life and, by definition,s carry a 2;5 [t(2;5)(p23;q35)] chromosomal translocation of the ALK gene resulting in overexpression of the ALK protein[4]. The ALK- subtype of ALCL usually occurs in middle age and has a worse prognosis[5]. An extranodal presentation is found in only 20% of the cases[6]. The most frequent extranodal involvement sites are the skin, lungs, bone, and liver[7,8], whereas the colon is rarely reported as being involved[3,9]. To the best of our knowledge, there have only been 9 such cases reported in 4 papers written in English[10-13]. Three of those reports were case reports, and no review has focused on this rare presentation. Therefore, in addition to reporting one case of ALCL, ALK- involving the colon and penis, we also conducted a literature review that showed some interesting clinical and pathological features of gastrointestinal ALCL, ALK-.

CASE PRESENTATION

Chief complaints

A 54-year-old male was admitted to the department of gastroenterology for abdominal pain. He presented with lower abdominal pain; frequent passing of stool, diarrhea and mucus; and recurrent oral ulcers.

History of present illness

The patient was a 54-year-old male with a history of a recurrent penile ulcer for 6 years. He presented with lower abdominal pain; frequent passing of stool, diarrhea and mucus; and recurrent oral ulcers. No additional sites of involvement were identified. CT enterography (CTE) and colonoscopy showed skip lesions and different sizes and shapes of ulcers in the colon. The lesions of the colon were biopsied for histological examination. The biopsy showed nonspecific ulcers of the colon. According to his history and auxiliary examinations, he was diagnosed with Behcet's disease (BD) and treated with prednisone. He was discharged in an improved condition. After one month, he was hospitalized in another hospital because of colon perforation. After operation, he was transferred to the rheumatology and immunology department. This time, bilateral inguinal lymph nodes were found enlarged. The lesion on the penis was biopsied for histological examination. The final

pathological diagnosis was ALCL, ALK-negative (ALCL, ALK-).

History of past illness
No past illnesses were documented.

Personal and family history
Unremarkable.

Auxiliary examination
CT enterography (CTE) showed abnormal thickening of the bowel walls at the cecum, ascending colon, transverse colon, and descending colon, and the intestinal wall showed obvious enhancement in the arterial stage (Figure 1). Colonoscopy showed skip lesions and different sizes and shapes of ulcers in the cecum, transverse colon, and descending colon (Figure 2). The lesion on the penis was biopsied for histological examination. HE staining showed infiltration of large lymphoid cells (Figure 3). Immunohistochemistry showed that the neoplastic cells were positive for CD2, CD3, CD10, CD30, LCA, and Mum-1. The expression of Ki-67 was 70% positive. The cells were negative for CD20, CD56, Bcl-2, Bcl-6, Pax-5, P40, P63, PCK, ALK-80, and EBER (Figure 3). The final pathological diagnosis was ALCL, ALK-negative (ALCL, ALK-).

FINAL DIAGNOSIS
Anaplasticlymphomakinase-negative anaplastic large cell lymphoma at IVE.

TREATMENT
The patient was treated with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy once.

OUTCOME AND FOLLOW-UP
However, the patient died of septic shock soon.

DISCUSSION
ALCL is a CD30+ positive T cell lymphoma with its own characteristic morphology and immunophenotype[14]. According to the expression of ALK, the WHO 2016 classification system divided ALCL into four entities: systemic ALK-positive ALCL (ALCL, ALK+), systemic ALK-negative ALCL (ALCL, ALK-), primary cutaneous ALCL (pC-ALCL), and breast implant-associated ALCL (BI-ALCL)[2]. ALCL, ALK- represents 15%-50% of the cases of systemic ALCL. While most cases of ALCL, ALK+ are seen in children, ALCL, ALK- is often found in adults[3]. ALCL, ALK+ is sensitive to chemotherapy and often has a better prognosis, but ALCL, ALK- always occurs in elderly patients with a poor clinical outcome[9]. ALCL, ALK- results in a worse prognosis than ALCL, ALK+, with 5-year survival rates of 50% and 70%, respectively[9,15]. ALCL, ALK- mainly involves the lymph nodes but approximately 20% of cases can also be found in extranodal sites[3]. Secondary involvement of ALCL, ALK- in the skin has to be distinguished from mucosa-associated lymphoid tissue lymphomas, including pC-ALCL and BD. The differential diagnosis is difficult and requires a comprehensive approach, including clinical evaluation, histopathologic evaluation, and determination of the immunophenotype[6]. The extranodal sites often include the skin, breast, lungs, bone, liver and gastrointestinal tract[3,9,16,17]. To the best of our knowledge, only one case reported pC-ALCL presenting as paraphimosis[18]. Our case is the second reported case of ALCL in the penis and the first one of systemic ALK-negative ALCL.

The incidence of primary intestinal lymphomas is very rare. Gastrointestinal lymphomas account for 20% of them, and most of them are mucosa-associated lymphoid tissue lymphomas[19,20]. We present a case of primary ALCL arising in the oral cavity, penis, and colon, which was initially misdiagnosed as BD. In 2013, the International Study Group criteria for BD presents a new criteria that ocular lesions, oral aphthosis and genital aphthosis are each assigned 2 points, while skin lesions, central nervous system involvement and vascular manifestations 1 point each[21]. A patient scoring ≥ 4 points is classified as having BD. So this patient just fit the criteria.

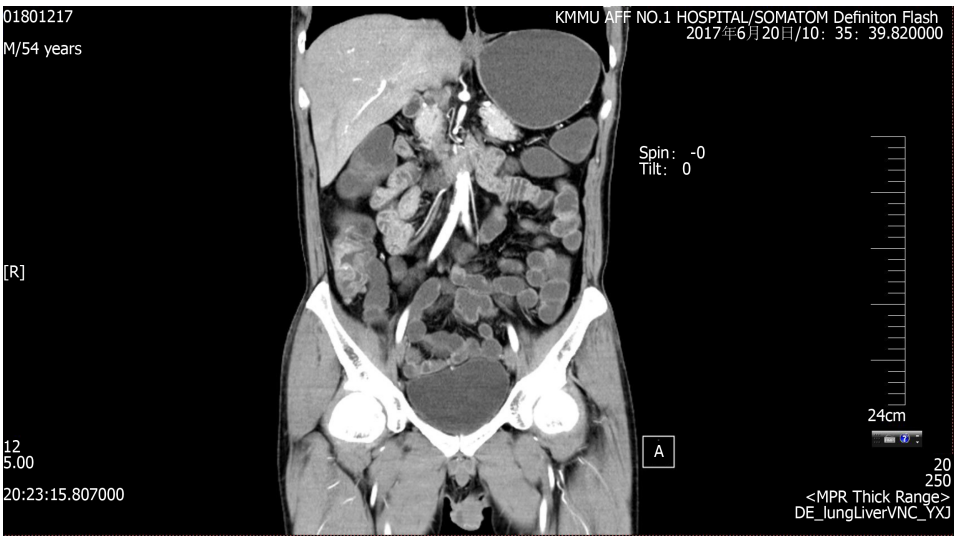

Figure 1 Computed tomography enterography. Irregular thickening of the intestinal wall was observed in the cecum, ascending colon, transverse colon and descending colon, which also showed skip lesions. The thickest part of the intestinal wall was approximately 16 mm, and the intestinal wall in the arterial enhancement stage showed obvious enhancement (unclear hierarchical boundary); small vessels in the mesangial side were tortuous and dilated (locally formed as a "wooden comb"); and the surrounding fat was slightly blurred. No obvious thickening was observed in the small intestine wall.

But finally, the morphologic and phenotypic features were found to be consistent with systemic ALCL, ALK-, at IVE. This may be because the presence of inflammation with neutrophil infiltration affects the mucosa in systemic ALCL[22]. Therefore, in our case, neutrophil infiltration may have been associated with the presence of large ulcers at multiple sites, as reported in Lapthanasupkul *et al*[23]. It is extremely rare for ALCL to initially present with gastrointestinal symptoms. Our review of the English language literature identified four papers that reported this disease, including nine case reports[10-12] (Table 1). Including the current case, the patients were eight males and two females (4:1). The median age was 66.3 years (ranging from 54 to 88 years). The main gastrointestinal sites involved were the esophagus in 1 case (10%), the stomach in 4 cases (40%), the jejunum in 1 case (10%), the terminal ileum in 2 cases (20%), and the colon in 2 cases (20%). The cases initially presented with abdominal pain, mass or diarrhea. Colonoscopy revealed a reddish ulcerative lesion with protrusion or different sizes and shapes of ulcers. After receiving six cycles of CHOP chemotherapy or other therapies, three patients achieved complete remission. The other seven patients died due to disease progression from 0.7 to 63 mo after the diagnosis.

CONCLUSION

In summary, there are some interesting clinicopathologic features associated with the gastrointestinal involvement of ALCL: (1) There is a male predominance; (2) The majority of the patients are more than 50 years old; (3) The patients uniformly present with gastrointestinal symptoms such as abdominal pain, mass or diarrhea; (4) The primary neoplasm is in the stomach; (5) Endoscopic examination often shows irregular ulcers; and (6) The most commonly used treatment is CHOP, but the prognosis is poor. Although limited by the number of cases available, our findings indicate that this group of ALCLs has an unusual clinical presentation and could pose a diagnostic challenge. Furthermore, a timely diagnosis and treatment are crucial to avoid disease progression. It is essential to establish a timely diagnosis of ALCL through pathological, immunohistological, and clinical evaluations[22]. We hope this review will bring attention to and help us understand the rare presentation of ALK-negative ALCL. In addition, gastrointestinal ALCL needs to be considered in the differential diagnosis even when autoimmune bowel disease is suspected, especially in older patients.

Table 1 Primary anaplastic lymphoma kinase negative anaplastic large cell lymphoma of the gastrointestinal tract in our current study and in the literature

Ref.	Gender;Age	Presenting symptom; impression	Primary site	Biopsy or surgery	Perforation	Marrow involvement	Treatment	Follow-up
Sakakibara *et al*[10], 2015	M 65	A painful hard mass in the left buttock.	Ascending colon	Colon biopsy	(-)	(-)	Six cycles of CHOP	Achieved complete remission
Tian *et al*[11], 2016	M 39	Epigastric pain with low-grade fever	Stomach	Stomach biopsy	(-)	(-)	Four cycles of CHOP, then two cycles of Hyper-CVAD/MA	Died 3 mo later
Zhang *et al*[12], 2017	M 82	Weakness	Stomach	Stomach biopsy	(-)	(-)	Brentuximab	Clinically improved
Lee *et al*[13], 2017	F 64	Not mentioned	Oesophagus	Segmental resection of distal oesophagus and proximal partial gastrectomy	(-)	(-)	Various regimens and transplantation after relapse	Died 63 mo later
	M 59	Not mentioned	Stomach	Partial gastrectomy	(-)	(-)	CHOP	No evidence of disease after 81 mo
	F 70	Epigastric pain with poor appetite	Stomach	Total gastrectomy and liver biopsy	(-)		CHOP and ESHAP	Died 21 mo later
	M 65	Fever	Jejunum	Segmental resection	(+)	(+) (focal)	Nil	Died 0.7 mo later
	M 88	Not mentioned	Terminal ileum	Segmental resection	(-)	(-)	CHOP	Alive with disease after 4 mo
	M 37	Not mentioned	Terminal ileum	Right hemicolectomy	(-)	Not done	Nil	Died 0.7 mo later
Current study	M 54	Lower abdominal pain and diarrhea	Colon	Penis biopsy	(+)	Not done	One cycle of CHOP	Died 1 mo later

CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisolone.

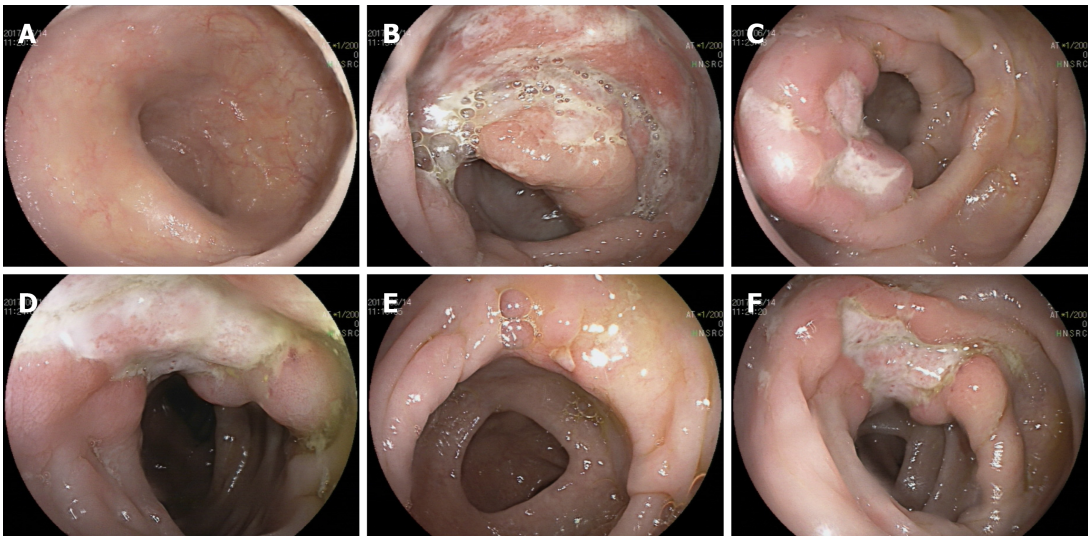

Figure 2 Colonoscopy. The mucosa in the ileocecal region, ascending colon, transverse colon and descending colon were scattered with ulcers of varying sizes, all covered with white moss and surrounded by mucosal hyperemia and edema, especially in the ileocecal region:A: Distal ileum; B: Ileocecal region; C: Ascending colon; D: Transverse colon; E: Descending colon; F: Descending colon.

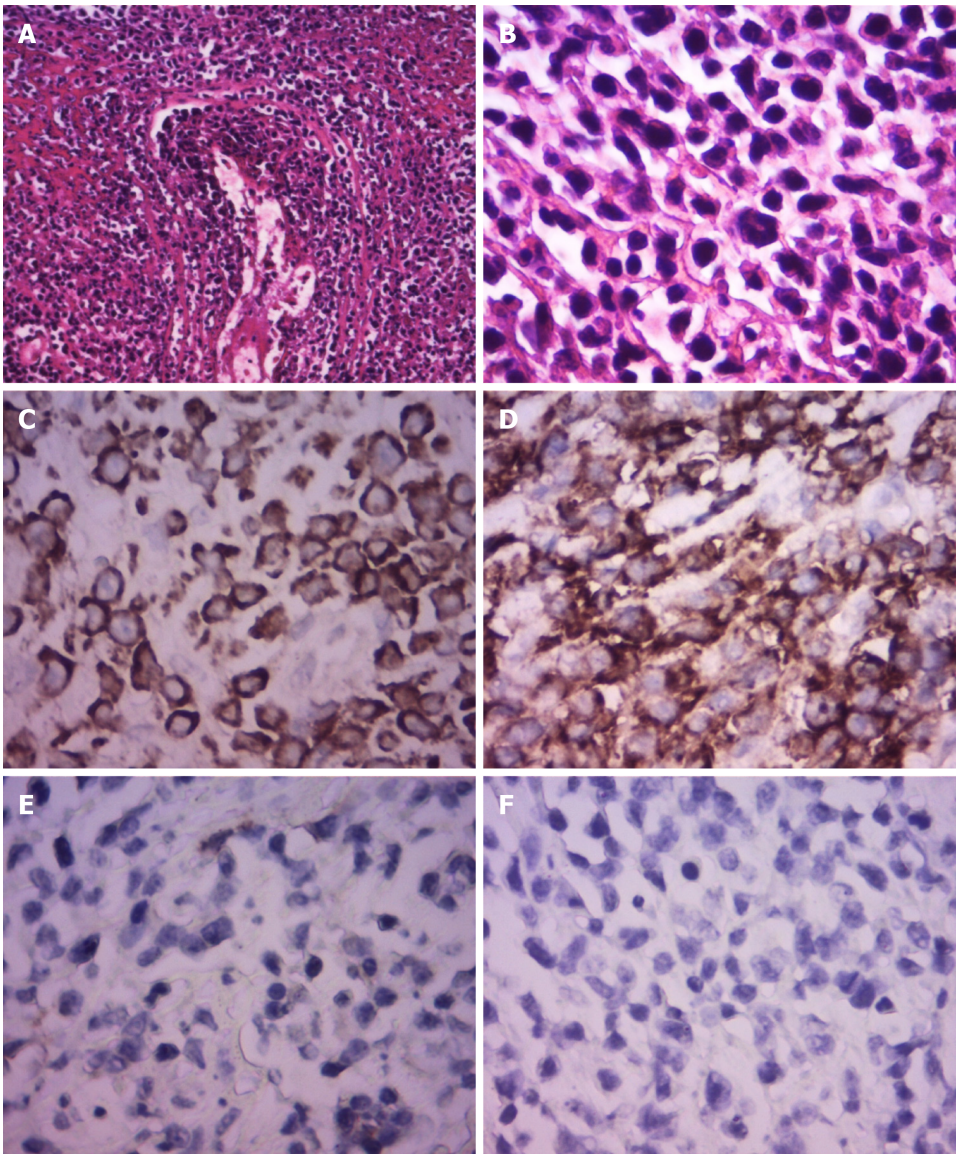

Figure 3 Pathological and immunohistological examination. Immunohistochemistry showed the neoplastic cells were positive for CD2, CD3, CD10, CD30, Ki67, LCA, and Mum-1. The cells were negative for CD20, Bcl-6, Bcl-2, Pax-5, P63, PCK, CD56, P40, ALK-80, and EBER. Pathological examination: A: x 100; B: x 400; Immunohistological examination: C: CD3 (+), x 400; D: CD30 (+), x 400; E: CD56 (-), x 400; F: ALK-80 (-), x 400.

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