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Case Report

Extranodal NK/T-cell lymphoma, nasal type: a case report of 7-year natural course and review of literature

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Abstract: We present our experience a vary case of Extranodal natural killer (NK)/T-cell lymphomas, nasal type (ENKL) who survived for 7 years, and review the recent advances on the differential diagnosis.

Keywords: Extranodal natural killer/T-cell lymphomas, Epstein-Barr virus, clinical features, prognosis

Case report

A 46-year-old man was admitted to our hospital with a 7-year history of recurrent diarrhea, abdominal pain, and fever. He complained of yellow loose paste stools 3 to 10 times per day 7 years prior to admission, accompanied with a little bit mucosanguineous feces, abdominal distension sometimes, and recurrent fever up to 41°C without cough. He was admitted in our hospital on Sept. 9th, 2008. The colonoscopy and pathological examination showed the non-specific enteritis and ulceration in transverse colon, which conformed to chronic ulcerative colitis. The capsule endoscopy showed the multiple ulcers in small intestine (**Figure 1**). The patient's symptoms improved after he received the treatment of Medrol and Pentasa. He also achieved good control of symptoms with tapering of Medrol to withdrawal after he discharged on Oct. 10th, 2008. The diarrhea was recurrent in 2012, accompanied with paroxysmal abdominal pain. He had being continually hospitalized in local hospital, and colonoscopy showed ulcerative colitis. On Apr. 15th, 2014, he was admitted to local hospital again, and been considered "incomplete ileus and ulcerative colitis". His symptoms improved after medical conservative treatment but he discharged till to Apr. 26th, 2014. The patient presented as having had abrupt abdominal pain at local emergency department on May 1st, 2014, so the doctor considered "ileal perforation, ulcerative colitis and acute diffuse peritonitis" and performed emergency laparoscopy-assisted partial small bowel resection and converted to open operation. He received anti-inflammation therapy after operation. Post-discharge there was still repeated diarrhea and abdominal pain. The patient had a fever up to 38.7°C 2 days ago, accompanied with chills but no cough. Then he came to our hospital for medical treatment. The patient had weight loss nearly 10 kg in recent 2 years.

Past history: The patient had open operation for partial intestinal resection because of ileal perforation in May 2014.

Marital and childbearing history, personal history, family history: no evidence of abnormality.

Physical examination

Body temperature 37.3°C; blood pressure 95/62 mmHg. Sober consciousness, weak spiritual condition, emaciation. No superficial lymph nodes enlargement. No icterus. An old surgeon's scar about 10 cm in the middle of the abdomen. Mild tenderness in right lower abdomen but otherwise unremarkable. No rebound tenderness. A little active borborygmus. No abdominal mass. No limbs edema.

Laboratory tests

Blood routine: leukocyte count 7.8×10E9/L, neutrophil (%) 72.9%, hemoglobin 76 g/L. Blood biochemistry: albumin 21.7 g/L, globulin 30.7

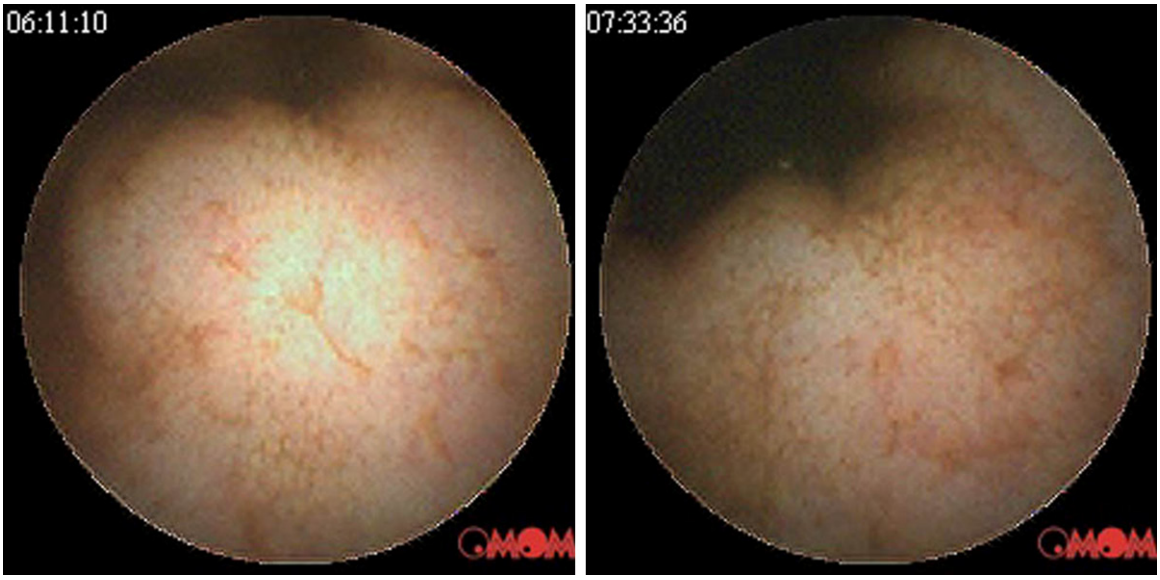

Figure 1. Sep. 2008, capsule endoscopy: multiple small ulcers in ileum.

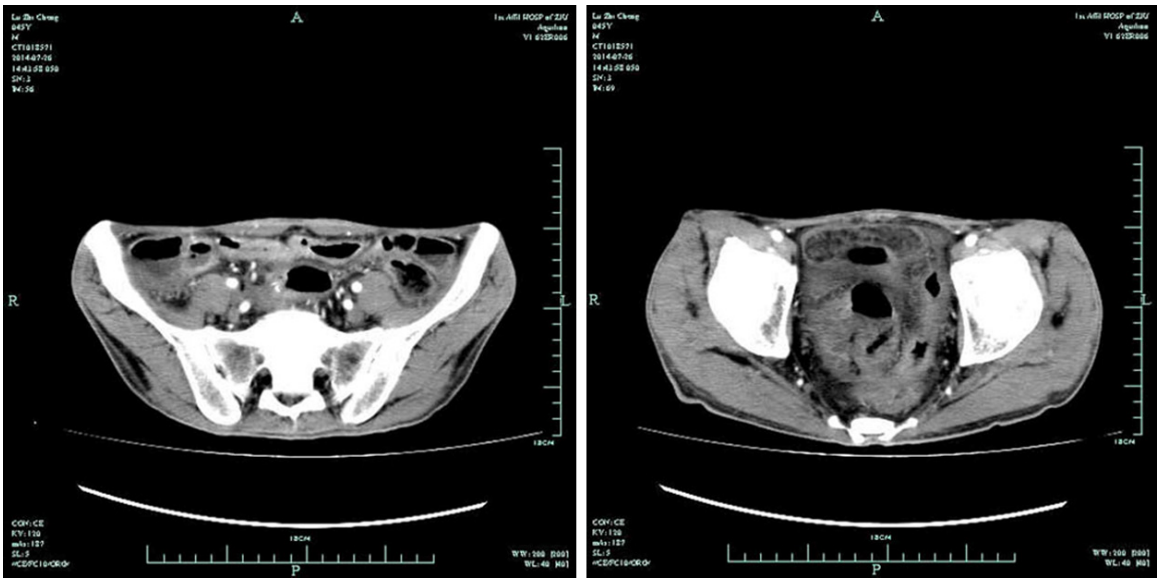

Figure 2. July 28th, 2014, the total abdomen plain scan CT and enhanced CT: thicken and edema of intestinal wall in partial transverse colon, descending colon and sigmoid colon; mucosa was significantly enhanced; the outside part of the intestinal wall and perienteric space was unclear; small lymph nodes in mesentery root and retroperitoneal region could be seen; considering inflammatory lesions.

g/L. Thyroid function: total triiodothyronine 0.75 nmol/L, free triiodothyronine 2.18 pmol/L. Stool routine + Occult blood test (OB): leukocyte 0-2, OB: +++. Erythrocyte sedimentation rate: 21 mm/hr. Super C-reactive protein: 66.3 mg/L. Cytomegalovirus(CMV) antibodies: CMV IgM (-), CMV IgG (+) 12.5 S/CO. EB virus antibodies: EB virus IgM (-), EB virus IgG (+) 10.8 S/CO. Serum β2 microglobulin 1299 μg/L. Procalcitonin 0.16 ng/ml. AMA, tumor marker examination, T-SPOT, MPO+PR3PCT, urine routines, ANA, ANCA, clostridium difficile culture, stool fungal culture, stool bacterial culture, blood culture: no evidence of abnormality.

Imageological examination

Chest X-ray film (PA position), ECG, B-ultrasonography of urinary system: no evidence of abnormality. B-ultrasonography of liver bladder

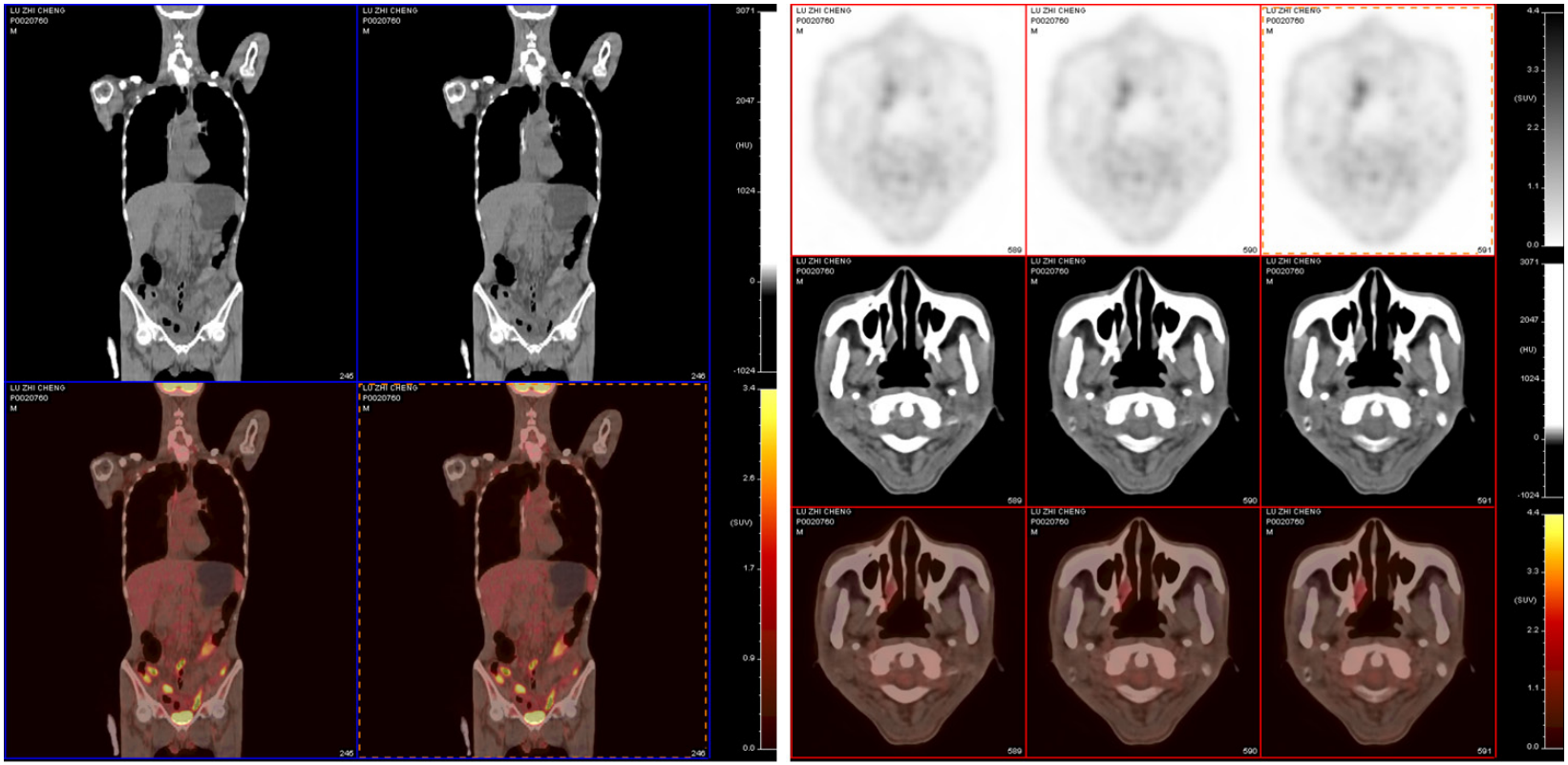

Figure 3. July 28th, 2014, PET-CT: postoperation of partial ileal resection because of ileal perforation, thicken of intestinal wall in lower small intestine, sigmoid flexure and rectal, accompanied with increased metabolism of FDG, splenomegaly with a little increased metabolism of FDG, considering lymphoma combining medical history and pathology; multiple lymph nodes enlargement in bilateral angulus mandibulae, para trachea, subcarina, left pulmonary hilum, retroperitoneal area, mesenteric of hypogastrium and pelvic cavity, accompanied with a little increased metabolism of FDG; soft tissue density lesion in right nasal cavity accompanied with a little increased metabolism of FDG.

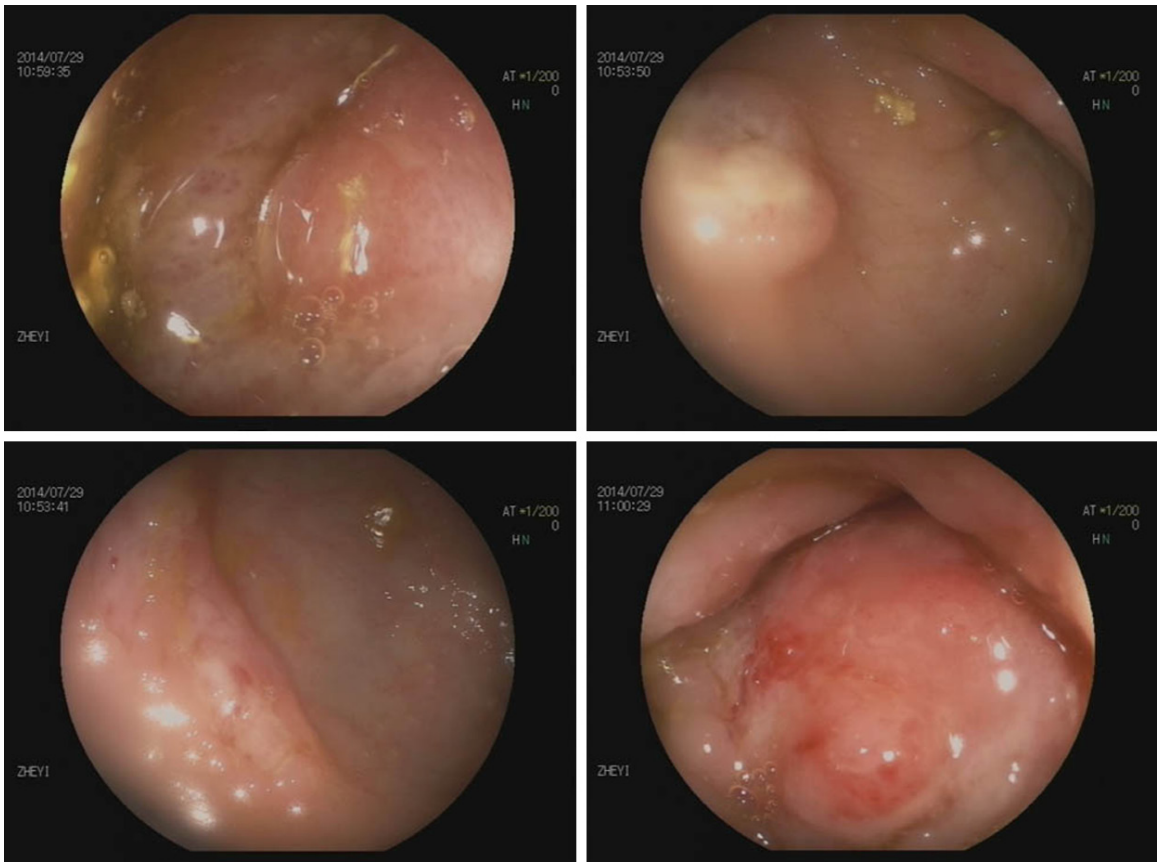

Figure 4. July 30th, 2014, Enteroscopy: significant stenosis in sigmoid colon. Multiple variable ulcers in sigmoid colon and rectum, accompanied with congestion and edema and significant erosion in surrounding mucosa.

spleen and pancreas: multiple polyps in gallbladder.

July 28th, 2014. The total abdomen plain scan CT and enhanced CT: thicken and edema of intestinal wall in partial transverse colon, descending colon and sigmoid colon, considering inflammatory lesions (**Figure 2**). PET-CT: postoperation of partial ileal resection because of ileal perforation, thicken of intestinal wall in lower small intestine, sigmoid flexure and rectal, accompanied with increased metabolism of FDG, splenomegaly with a little increased metabolism of FDG, considering lymphoma combining medical history and pathology; multiple lymph nodes enlargement in bilateral angulus mandibulae, para trachea, subcarina, left pulmonary hilum, retroperitoneal area, mesenteric of hypogastrium and pelvic cavity, accompanied with a little increased metabolism of FDG; soft tissue density lesion in right nasal cavity accompanied with a little increased metabolism of FDG, considering inflammatory firstly (**Figure 3**).

Aug. 5th, 2014. Chest plain scan CT: middle lobe of right lung small nodules; pleural effusion on the left; left lower lobe segmental pulmonary atelectasis. Echocardiography: left ventricle diastole function declined; mild tricuspid regurgitation; a little pericardial effusion.

Endoscope and histological examination

Bone marrow biopsy: active proliferation of bone marrow hematopoietic tissue.

July 30th, 2014. Enteroscopy: significant stenosis in sigmoid colon. Multiple variable ulcers in sigmoid colon and rectum, accompanied with congestion and edema and significant erosion in surrounding mucosa (**Figure 4**). Pathological diagnosis: (sigmoid colon) non-Hodgkin lymphoma (extranodal NK/T-cell lymphoma, nasal type). Immunohistochemical staining: CD2 (+), CD3 (-), CD4 (+), CD5 (-), CD7 (-), CD8 (-), CD20 (-), CD56 (+), Bcl-6 (-), CD21 (-), EBER (+), Ki-67 (+, 80%), PAX5 (-), CD68 (-), acid-fast bacilli (-); large necrosis in intestinal mucosa, medium-

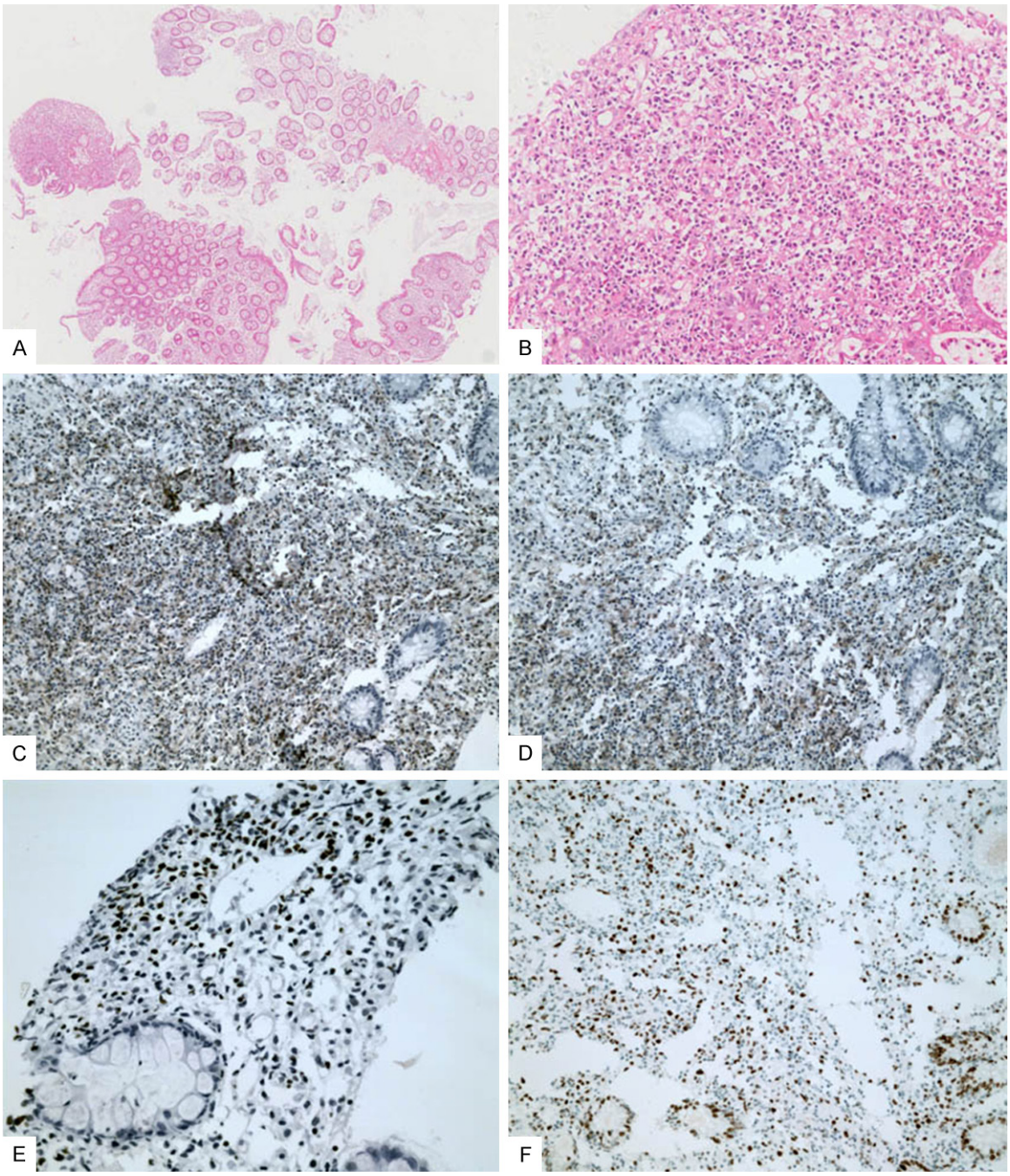

Figure 5. 2008, colonscopy and pathological examination in local hospital. (A, B) HE staining. (C-F) Immunohistochemical staining. CD2 (+) (C); CD56 (+) (D); EBER (+) (E); Ki67 (+, 50%) (F).

sized atypical lymphoid cells infiltration and vascular invasion (**Figure 6**).

After a definite diagnosis, we reviewed the pathology the intestinal biopsy specimens in local hospitals as follows:

2008. Enteroscopy and pathological examination: non-Hodgkin lymphoma (extranodal NK/T-cell lymphoma, nasal type). Immunohistochemical staining: CD2 (+), CD3 (-), CD8 (-), CD20 (-), CD56 (+), EBER (+), Ki-67 (+, 50%) (**Figure 5**).

May 2014. Pathology of ileal perforation surgery: (ileal) non-Hodgkin lymphoma (extranodal NK/T-cell lymphoma, nasal type). Immunohistochemical staining: CD2 (+), CD3 (-), CD4 (+),

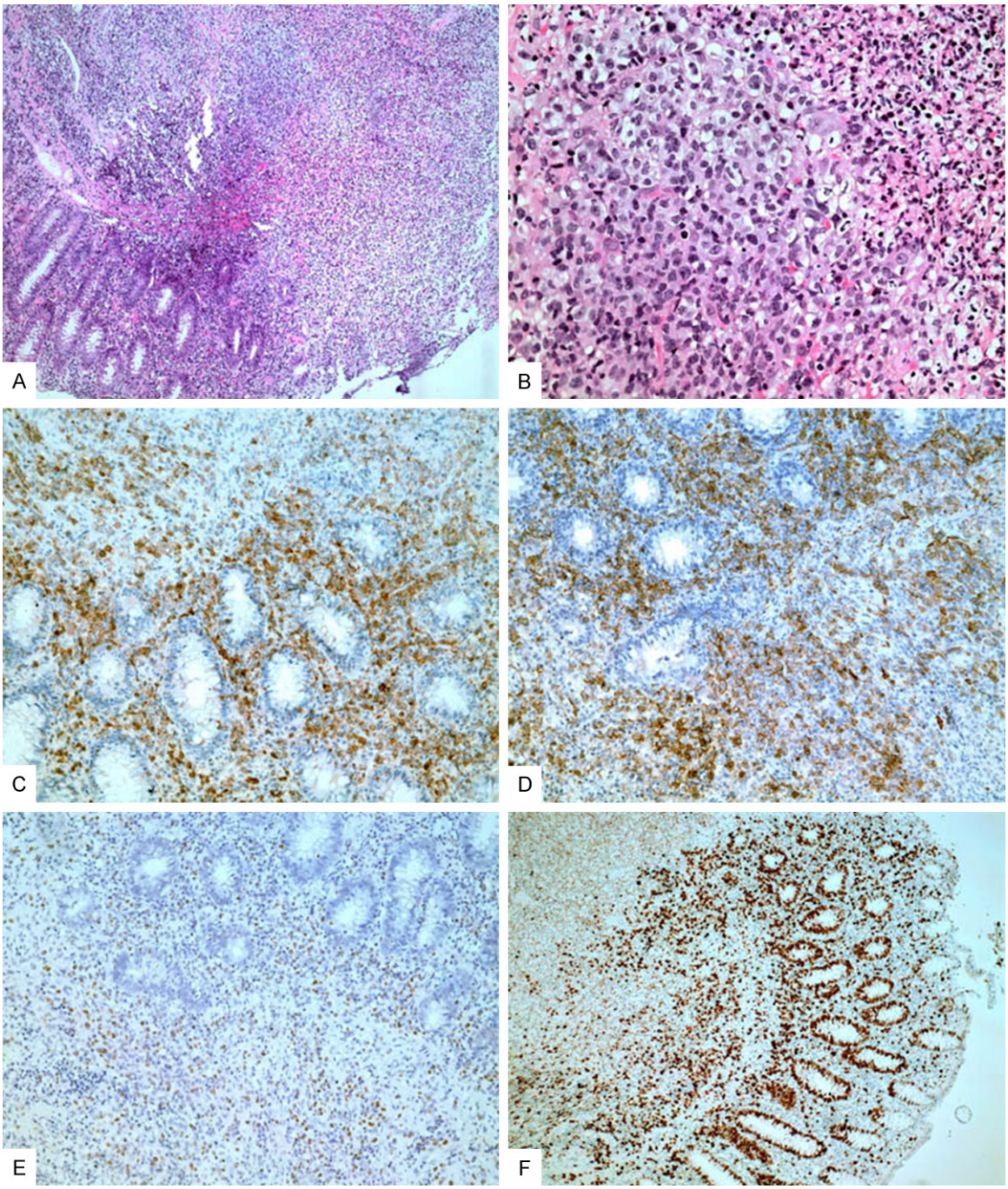

Figure 6. July 30th, 2014, colonscopy and pathological examination. (A, B) HE staining. (C-F) Immunohistochemical staining. CD2 (+) (C); CD56 (+) (D); EBER (+) (E); Ki67 (+, 80%) (F).

CD8 (-), CD20 (-), CD56 (+), EBER (+), Ki-67 (+, 60%).

Diagnosis

Non-hodgkin lymphoma (extranodal NK/T-cell lymphoma, nasal type, IV stage), post-operation of ileal perforation.

Treatment

The patient had continued hyperthermia and black loose stools when he was hospitalized, which revealed infection. He was treated with levofloxacin, turning into sulperazone and metronidazole injection later. Besides he also received other treatment such as transfusion

of red blood cell suspension and albumin, pentasa, hemostasis, parenteral nutrition, symptomatic treatment. However, there were still repeated mucosanguineous feces and continued hyperthermia. The confirmed diagnosis was made on Aug. 7th, 2014, and he took improved SMILE chemotherapy regimens (IFO 2.0dl, 3, VP16 100 mg d2, 4, DXM 20mg 1-3, L-ASP 10000U qod d8) twice, but the therapeutic effect was poor. The patient died on Oct. 11th, 2014.

Discussion

Etiology and pathogenesis

Extranodal natural killer (NK)/T-cell lymphomas, nasal type (ENKL) is a predominantly extranodal lymphoma, mainly occurring in the nasal-paranasal area, skin/soft tissue, especially occurring in the GI tract. According to the World Health Organization classification of lymphoid malignancies, NK/T-L is classified as a mature T-cell and NK-cell neoplasm [1].

The most important factor for lymphomagenesis of ENKL is the Epstein-Barr virus (EBV). EBV infection is regarded as a hallmark of this type of lymphoma. Clonal EBV is found in virtually all ENKLs. Cell-free fragmented EBV-DNA is released from lymphoma cells during apoptotic proliferation [2].

Angiocentricity and angioinvasion of NK/T-L leading to ischemic change may further destroy the bowel wall and result in perforation. Serum CA-125 level, which is solely an indicator of perforation, may also help the prognostic evaluation [1].

Epidemiology

Extranodal NK/T-L has a greater prevalence in East Asian and Latin American countries than in other parts of the world. Extranodal NK/T-L accounts for 2-8% of non-Hodgkin lymphomas in Asia [3, 4], with the rate increasing in the order of Japan, Taiwan, HongKong, and Korea. The origin of the tumor was the nose and paranasal area in more than 80% of the patients [1]. About 60% to 90% of extranodal natural killer T-cell lymphoma (NKTCL) occurs in the nasal cavity and its adjacent sites; other sites where they occur are the skin, testis, gastrointestine, and muscles [5].

Clinical features

The prognosis of nasal NK/T-cell lymphoma is extremely poor [2], especially when other systemic sites are involved. Cheung et al reported that the median overall survival rate of patients with NK/T-cell lymphoma is 12.5 months [6]. In China, the median age was 33 years and the median survival was 2.8-7 months [3, 5]. Jiang et al reported that patients had a median age of 37 years. Thirty-five of the patients were men (74.5%). The nonspecific clinical manifestations include fever (78.7%), abdominal pain (76.6%), intestinal perforation (36.2%). Almost all patients showed ulcerative lesions; the most common site of involvement was the colon (27/47; 57.4%), followed by the jejunoileum and ileocecum (14/47; 29.8%).

Diagnosis

Endoscopy shows that: focal or multifocal ulcers, stenosis of intestine wall, or occupying lesions. The pathologic findings may show atypical pleomorphic lymphoma cells infiltration of an angiocentric and/or angioinfiltrative character [6]. Immunohistochemical staining: the lymphoma cells express NK cell markers, including CD2, cytoplasmic CD3, CD7, and CD56; surface CD3, CD5, CD4, CD5, CD8, CD20, and T-cell receptor (TCR) are negative; cytotoxic molecules such as TIA-1, granzyme B, and perforin are also positive in ENKL; Ki-67 positive index is high; in nuclear situ hybridization for EBER is positive [2]. Because the surface of these lesions tends to be associated with crusting and necrotic tissue, the diagnosis of NK/T-cell lymphoma can be extremely difficult with only punch biopsy. This difficulty may explain why some hospitals miss the diagnosis. Deep biopsy or excisional biopsy is often needed to diagnose this disease.

Differential diagnosis

Crohn's disease: Aphthous ulcers, stricture, cobblestone appearance, skip lesions, longitudinal ulcers and microgranulomas are helpful to diagnosis of CD. So the endoscopy and histological features can contribute to differential diagnosis of CD and NKTCL [7, 8].

Lymphomatoid gastroenteropathy (Takeuchi's disease): This disease is characterized by localized proliferation of NK cells, mostly in the

stomach, but less frequently in the intestine. Patients do not show specific symptoms, and most are found by chance. Many of them accompany gastric cancer. Macroscopic findings show protruded lesion(s) in the stomach of approximately 1 cm diameter with or without depression or ulcers. A sheet proliferation of NK cells is found in biopsy specimens but necrotic pictures are not seen. EBV is negative, and can be a hallmark of differential diagnosis from ENKL. Lymphoepithelioid lesions are occasionally observed. Eosinophilic granules are found in proliferating NK cells, but their nature is uncertain. Association with Helicobacter pylori, which is often recognized, remains unclear. The lesions usually disappear without any medications, but infrequently experience recurrence. The most important point for this disease is to avoid chemotherapy for lymphoma and to watchfully observe [2].

Chronic NK cell lymphocytosis: CNKL is characterized by a chronic increase of peripheral blood NK cells without lymphadenopathy or organomegaly. This disease is essentially non-neoplastic nature, and does not show any cytogenetic abnormalities. EBV is usually undetectable in CNKL, hence the examination of EBV may help the differential diagnosis. CNKL is sometimes associated with reactive conditions against viral infections or underlying solid tumors [2].

EBV-associated T/NK-cell lymphoproliferative disease (T/NK-LPD): EBV-associated T/NK-cell lymphoproliferative disease (T/NK-LPD) is defined as a systemic illness characterized by the systemic distribution of EBV_clones beyond the clinical categorization currently proposed as CAEBV, HLH, severe mosquito bite allergy, and hydroa vacciniforme, the distinction of which are differentiated based on clinical manifestations [9]. This disease is rare, associated with high morbidity and mortality, and appears to be more prevalent in East Asian countries. EBV-T/NK LPD includes polyclonal, oligoclonal, and monoclonal proliferation of cytotoxic T and/or NK cells [10].

A clinicopathological categorization of EBV-T/NK LPD is proposed, based on pathological evaluation and molecular data, as follows: (i) category A1, polymorphic LPD without clonal proliferation of EBV-infected cells; (ii) category A2, polymorphic LPD with clonal proliferation of EBV-infected cells; (iii) category A3, monomorphic LPD (either peripheral T-cell lymphoma or NK cell lymphoma/leukemia) with clonal proliferation of EBV-infected cells; and (iv) category B, monomorphic LPD (peripheral T-cell lymphoma) with clonal proliferation of EBV infected cells and fulminant course in a short time from an apparent primary EBV infection. Categories A1, A2, and A3 possibly constitute a continuous spectrum and together are equivalent to CAEBV. Category B is the exact equivalent of infantile fulminant EBV-associated T-LPD [10]. Underlying this categorization system is the notion that this disease constitutes a continuous spectrum, which makes it sometimes difficult to recognize and accounts for the gray area between this disorder and other WHO-defined lymphomas. Further studies are required to elucidate its nature and its relationship to other types of lymphomas [11].

Compared with more well-defined diseases such as extranodal NK/T-cell lymphoma and aggressive NK cell leukemia, systemic EBV-positive T-cell LPD patients were mainly children and young adults and presented with acute illness with a fulminant clinical course, similar to aggressive NK cell leukemia, with death in a matter of weeks [10]. Additionally, some patients develop oligoclonal or monoclonal lymphoproliferation, including T-cell or NK-cell proliferation, eventually resulting in T-cell or NK-cell malignant lymphomas [12, 13]. Hiroshi Kimura et al found that most of the patients with EBV_ T/NK-LPDs had clonality of EBV-infected cells. 6 patients who were clinically categorized as CAEBV NK-cell type (4 cases) and T-cell type (2 cases) developed ENKL. These results indicate that patients with clonally expanding EBV-infected T or NK cells in EBV_ T/NKLPD eventually develop overt leukemia and lymphoma [9]. However, if the clinical data are absent regarding the prodromal phase of expansion of EBV_T/NK–cells with variable clonality, we cannot discriminate systemic diseases such as ANKL and extranasal ENKL from EBV_NK-LPDs, because EBV_proliferating cells are indistinguishable in morphology and phenotype. Recently, this issue was highlighted by Takahashi et al [14]. It is clear that some EBV-T/NK-LPD cases are characterized by CD56+ cytotoxic molecules+ and by EBV+ type, which is phenotypically identical to that of aggressive NK-cell leukemia/lymphoma and extranodal T/

NK-cell lymphoma, nasal type. Clinicopathological re-evaluation of the latter entities is needed for a further understanding of the interrelationship among those diseases [11].

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Disclosure of conflict of interest

None.

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