Monomorphic Epitheliotropic Intestinal T Cell Lymphoma With Lower Gastrointestinal Hemorrhage: A Case Report and Literature Review

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Case Report

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Abstract

Enteropathy-associated T cell lymphoma(EATL) is a kind of malignant lymphoma with strong invasiveness. Due to poor effect of conventional symptomatic treatment, the prognosis is not as good as other T-cell lymphomas. A 63-year-old man was admitted to our hospital due to hematochezia. No definite cause was found by electronic gastroscopy and electronic colonoscopy. After symptomatic treatment, the patient's condition did not show significant remission. However, he refused further examination and was discharged. Two months later, the man was admitted to our hospital again due to hematochezia. The site of the lesion was found by capsule endoscopy and small intestinal endoscopy, and the nature of the lesion was confirmed by immunohistochemistry. The patient received chemotherapy and autologous stem cell transplantation after a definite diagnosis. No recurrence or metastasis has been found in an 18-months follow-up after treatment.

Background

Lymphoma is a class of hematological malignancies that arise from lymphoid tissue, including Hodgkin lymphoma and non-Hodgkin lymphoma. The digestive tract is the most common site for extranodal non-Hodgkin lymphoma. Diffuse large B-cell type, mantle cell type and follicular type were the main histological classification, while T cell lymphoma is rare. Enteropathy-associated T cell lymphoma(EATL) is a type of non-Hodgkin lymphoma, which accounts for only 5.4% of all lymphomas, compared with 9.1% in Europe and 1.9% in Asia, median morbidity age is about 60 years old, it’s more common in men than women(1, 2). It is often misdiagnosed due to non-specific with minor endoscopic abnormalities. The diagnosis is mainly based on histological observation, immunohistochemical staining, EBER detection and gene rearrangement detection. Currently, there is a lack of standard and consensus for the treatment of EATL, most of which are based on expert opinion and exploratory therapy. In this paper, a case of enteropathy-associated T cell lymphoma type II (monomorphic epitheliotropic intestinal T-cell lymphoma) with recurrent lower gastrointestinal hemorrhage as the main symptom was reported. The diagnosis methods, treatment regimens and clinical effects of enteropathy-associated T cell lymphoma reported in recent years were also summarized and analyzed.

Case Presentation

On July 21, 2019, a 63-year-old man was admitted to our hospital with recurrent black stool for 2 days. Two days ago, the patient had no obvious inducement to defecate melena, accompanied by dizziness and fatigue, and immediately went to the local hospital to see a doctor. The symptoms were not relieved after taking hemostatic drugs in the local hospital and transferred to the emergency department of Xianyang Central Hospital for further diagnosis and treatment afterward. Electronic gastroscopy showed scattered flaky erosion of the gastric fundus, punctate erythema of the gastric body, and the diagnosis was chronic non-atrophic gastritis with erosion. Electronic colonoscopy showed scattered punctate erosion of the ileocecal mucosa, and the diagnosis was ileocecal valvular inflammation. No obvious abnormality was found in enhanced CT of the chest and abdomen. The patient refused further

examination and was discharged from the hospital. On September 4, 2019, the patient was admitted to our hospital again with recurrent black stool for 2 months. Capsule endoscopy (Fig. 1A) showed that the capsule entered the duodenum through the pylorus in 37 minutes and 26 seconds, the bulbar mucosa was congested and edematous, then the capsule quickly entered the jejunum, although the intestinal preparation was poor, multiple deep basement depressions could be seen in the local jejunal mucosa. Accordingly, diagnosis of ulceration and tumor may be considered. Single balloon enteroscopy (Fig. 1B) was performed and 6 biopsies were taken. Under enteroscopy, large patches of ulcerative lesions about 50cm from the great nipple of the duodenum were seen, covered with gray-and-white moss, with active blood oozing, and the biopsy was tough. Considering the possibility of Crohn's disease and lymphoma, the biopsy is recommended to determine the nature. Morphological observation of biopsy tissue (Fig. 1C,1D): there was mainly lymphocyte infiltration in jejunal mucosa, most of them were single round lymphocytes, a few of them were nuclear-twisted cells, the cells were equal, heteromorphic, lightly stained cytoplasm, obvious nucleolus and mitosis. Immunohistochemical staining (Fig. 2A-2D): lymphocyte CD3 (Fig. 2A), CD8 (Fig. 2B), CD56 (Fig. 2C) were positive, CD20 (B cell expression marker) and in situ hybridizations EBER were negative, the proliferation index of Ki-67(Fig. 2D) was 80%. The pathological results were consistent with T-cell lymphoma, monomorphic epitheliotropic T-cell lymphoma (type II of enteropathy-associated T cell lymphoma) was considered in the classification. After a clear diagnosis, he was transferred to Xijing Hospital of Air Force military Medical University for chemotherapy and autologous stem cell transplantation. No recurrence or metastasis has been found in an 18-months follow-up after treatment.

Discussion And Conclusion

In 2001, the World Health Organization (WHO) divided EATL into two types: intestinal T-cell lymphoma and enteropathy-associated T-cell lymphoma. Owing to many subtypes of T-cell lymphoma show the symptoms of intestinal diseases, the differential diagnosis between EATL and other T-cell lymphomas was not clear. In 2008, WHO defined EATL more strictly and divided EATL into type Ⅰ and type Ⅱ, celiac disease and the positive expression of HLA-DQA1*0501, HLA-DQB1*0201 gene were associated with type I. As a monomorphic variant of type I, type II had unique cell morphology and immunophenotype(3). The classification of lymphoid tumors was revised by WHO in 2016, and the distinction between type Ⅰ and type Ⅱ of EATL is clearer, type II of EATL is officially named monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)(4).

EATL originates from intraepithelial lymphocytes (IELs), which is different from the origin cells of peripheral T-cell lymphoma, the T-cell subsets of EATL are mainly composed of γδ- T cell, which has more complex phenotypes, Overexpression of NK like cytotoxicity and interferon- γ signaling pathway is an important manifestation(5). Moffitt(6) found that the overexpression of interferon-γ signaling pathway is more obvious in type I EATL, which is consistent with the increase of interferon-γ secretion in patients with chylorrhea. Most genes in MEITL are involved in the natural killer-like cytotoxicity pathway. In terms of chromosome changes, a series of genomic hybridization analyses in Asia and Western countries

showed some similarities, EATL often shows amplification of chromosome 1q, 5q, 7q, 8q and 9q, and deletion of 8p, 9p and 13q(6, 7).

The differentiation of EATL types is mainly based on the cell morphology and immunophenotype, the tumor cells of type I EATL are medium or large-sized and diversified in morphology, immunophenotypes expressions are usually CD3 $^{+}$, CD43 $^{+}$, CD5 $^{-}$, CD7 $^{+}$, CD8 $^{\pm}$, CD4^{-}, CD103 $^{+}$, TCR $^{\pm}$ with chromosome 1q and 5q amplification, the gene expression of STAT3, STAT5A, IRF1 and IRF4 is higher in type I than in type II (4). The high expression of transglutaminase 2 (TGM 2) is closely related to chylorrhea in type I, insisting on a gluten-free diet is an important method to improve prognosis (8). MEITL is not closely related to celiac disease, the immunophenotype expressions of MEITL are often CD8 $^{+}$, CD56 $^{+}$, TIA-1 $^{+}$ with chromosome 8q amplification. The tumor cells are small and medium-sized, the nucleolus is darkly stained with round mononuclear cells and accompanied by nuclear division or necrosis, MAPK signaling is up-regulated, FASLG, SYK and TGBR1 genes are highly expressed (7, 9).

The onset of EATL is relatively occult. Half of the patients only have symptoms such as abdominal pain and diarrhea in the early stage, and most of them are hospitalized with acute intestinal obstruction or intestinal perforation in the late stage. In this case, gastrointestinal bleeding was the main clinical manifestation in both admissions, accounting for about 10% of the clinical features. During the first hospitalization, the patient's condition did not appear obvious remission after symptomatic treatment such as acid suppression and gastric protection, anti-inflammatory hemostasis, anti-infection, maintenance of water and electrolyte balance. However, the patient refused further treatment, resulting in delayed diagnosis and missed the best period of treatment. Most EATL lesions occur in the jejunum or ileum, and it is difficult to accurately detect the lesion site by electronic gastroscope and colonoscopy. Although some studies have shown that small intestinal CT enterography (CTE) can clearly show the abnormal changes of intestinal wall and extra-intestinal cavity, it is not as good as small intestinal endoscopy and capsule endoscopy to directly observe tissue lesions, and obtain more disease information and diagnostic ideas(10). Local erosion, ulcer and mass are the common manifestations of EATL under endoscopy. It can present segmental multiple lesions, often involving mesenteric lymph nodes, liver, spleen, lung and other parts, resulting in corresponding systemic changes. The histological observation of EATL is greatly affected by the location of biopsy. If the location of biopsy tissue is shallower than that of the lamina propria and mucosal muscular layer, it may only show crypt hyperplasia or gland atrophy, and tumor cells are often mixed with tissue cells, plasma cells and eosinophils. This mixed infiltration of cancer and inflammation will cover up tumor cells and greatly increase the probability of misdiagnosis. The preliminary diagnosis is mostly misdiagnosed as peptic ulcer, digestive tract adenocarcinoma, inflammatory bowel disease, Behcet syndrome, intestinal tuberculosis and other abdominal diseases. Multiple endoscopic and biopsy examinations were performed to determine the nature of the disease, and multidisciplinary discussions were actively carried out with the pathology and imaging departments. The improvement of immunohistochemistry and gene rearrangement tests is the key means to avoid a missed diagnosis of lymphoma.

In addition to the identification with abdominal diseases, MEITL also needs to be distinguished from type I EATL, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), B-cell lymphoma, extranodal nasal NK / T-cell lymphoma (ENKTL) and other lymphological diseases.

Among them, the more important is the differential diagnosis with indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. Since the incidence of indolent T-cell lymphoproliferative disorder of the gastrointestinal tract is relatively low, the studies are mostly concentrated in a small number of case reports. In 2017, WHO classified it as a new temporary entity into the classification of lymphatic tumors(11). The incidence sites are mainly concentrated in the small intestine and colon, and the incidence rates of esophagus and stomach are low, which overlaps with the common incidence sites of EATL(12). Superficial erosion and polypoid degeneration are common manifestations of indolent T-cell lymphoproliferative disorder of the gastrointestinal tract under endoscopy. Compared with EATL, EATL is less invasive and has few tumors infiltrating the whole intestinal wall(8).

Most of the immunophenotypes are $CD3^+$, $CD4^+$, $CD8^+$, TIA-1^+, $CD56^-$, $CD30^-$, Ki-67 cell proliferation index is less than 10 %, which are often accompanied by TCRβ or γ rearrangement, but there is no mutation of STAT3, STAT5B, SETD2 and other genes in EATL(13). Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract has poor response to conventional chemotherapy, but steroids can improve symptoms. Due to the slow progression of the disease and the low probability of transforming into invasive lymphoma, the survival time of patients is often more than ten years.

EATL is a complex disease affected by multiple genes which have strong invasiveness, poor effect of conventional symptomatic treatment and poor prognosis than other T cell lymphomas. Mutations in DNA damage response and repair genes (TP53, BCL11B, BRIP1), apoptosis-related genes DAPK3 and cell cycle transcription factor BBX frequently occur in EATL(1, 6). In the past, most patients were treated with surgery combined with systemic chemotherapy drugs. However, due to the frequent spread of tumor cells and more tumor-infiltrating tissue, complete resection is almost impossible, and the incidence of postoperative complications is high, surgical treatment often has little benefit(14). CHOP regimen based on anthracycline (cyclophosphamide, doxorubicin, vincristine, prednisolone) is the most commonly used chemotherapy regimen for EATL, but it has serious toxic and side effects, and most EATL is less sensitive to chemotherapy(15, 16). Although the immunophenotypes of EATL patients with type I are different from those of MEITL patients, the development of tumor cells still follows similar genetic pathways. SETD 2 gene is the most common silent gene in EATL, and JAK-STAT and GPCR signaling pathways are the most frequently mutated pathways(23). Targeted regulation of these sites may be a potential treatment for EATL in the future. In recent years, CVAD regimen (cyclophosphamide, vincristine, doxorubicin, dexamethasone), autologous stem cell transplantation(ASCT), histone deacetylase inhibitor, anti-CD 52 antibody, and other drugs have also been used in the treatment of EATL. Autologous stem cell transplantation can significantly improve the prognosis of EATL, prolong progression-free survival and overall survival(16–22). Due to the lack of relevant treatment standards and consensus on EATL, most treatments are based on expert advice and exploratory treatment. Combined treatment including surgical resection, systemic chemotherapy, and autologous stem cell transplantation is an effective way to

improve the therapeutic effect. If EATL patients were successfully treated with autologous stem cell transplantation, the total remission rate (ORR), progression-free survival time (PFS) and total survival time (OS) were comparable to those of other types of peripheral T-cell lymphoma (Table 1). In addition, car-t is an important method for the treatment of recurrent B-cell lymphoma with high clinical response rate. In recent studies, it was found that car-t can achieve long-term remission of the disease in the treatment of recurrent EATL that cannot undergo ASCT(24). Based on the gradual exploration of prospective clinical trials, we believe that the treatment of EATL will continue to perfect, and the survival time and quality of patients will continue to be improved.

Table 1
Treatment and follow-up results of enteropathy-associated T cell lymphoma

Project	Figure	Type	Treatment	PFS	OS
Sieniawski et al.[16]	26	EATL and	IVE/MTX-ASCT	5 years52%	5 years 60%
	31	EATL and	Chop	5 years 22%	5 years 22%
Phillips et al.[18]	11	EATL and	IVE-MTX-ASCT	1 year 45%	1 year 45%
Gale et al.[14]	31	EATL and	Chemotherapy, surgery	1 year 19.4%5 years 3.2%	1 year 38.7%5 years 19.7%
Mark et al.[19]	6	EATL and	Chemotherapy, surgery and ASCT		1 year 83.3%3 years 50%
Jantunen et al.[20]	44	EATL and	Chemotherapy and ASCT	4 years 54%	4 years 59%
Francesco et al.[21]	21	EATL and	Chop and ASCT	5 years 38%	5 years 48%
Tse et al.[22]	36	EATL	Chemotherapy, surgery and ASCT	1 year 21% median 1 month	1 years 36% median 7 months
Petula et al.[15]	5	EATL	Chop, surgery and ASCT		1 year 100%5 years 33%
	19	EATL	Chop, surgery		1 year 73%5 years 14%
	12	EATL	Chop		1 year 17%5 years 0%
	12	EATL	Surgery		1 year 17%5 years 8%

Table 2

Timeline of diagnosis and treatment process

Time	Events
July 21, 2019	The patient went to the local hospital with defecating black stool.
July 24, 2019	The patient was transferred to Xianyang Central Hospital.
August 1, 2019	The patient refused further examination, was discharged from the Xianyang Central Hospital.
September 4, 2019	The patient returned to Xianyang Central Hospital with defecating black stool.
September 20, 2019	The pathological results came out, monomorphic epitheliotropic T-cell lymphoma was considered.
September 22, 2019	The patient was transferred to Xijing Hospital of Air Force military Medical University for further treatment.
March 10, 2021	No recurrence or metastasis has been found in an 18-months follow-up after treatment.

Abbreviations

EATL: Enteropathy-associated T cell lymphoma; MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma; ASCT: autologous stem cell transplantation

Declarations

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Date availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Authors contributions

Corresponding author: Lin Yang. Preparation of graphical material: Xiao-Yan Ma, Rui-Ni Li. post-processing and completed the manuscript: Cheng Zhou, Hai-Juan Xiao, Yu Fang. All authors contributed

to the article and approved the submitted version.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent for publication

Informed consent was obtained from the patient.

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Figures

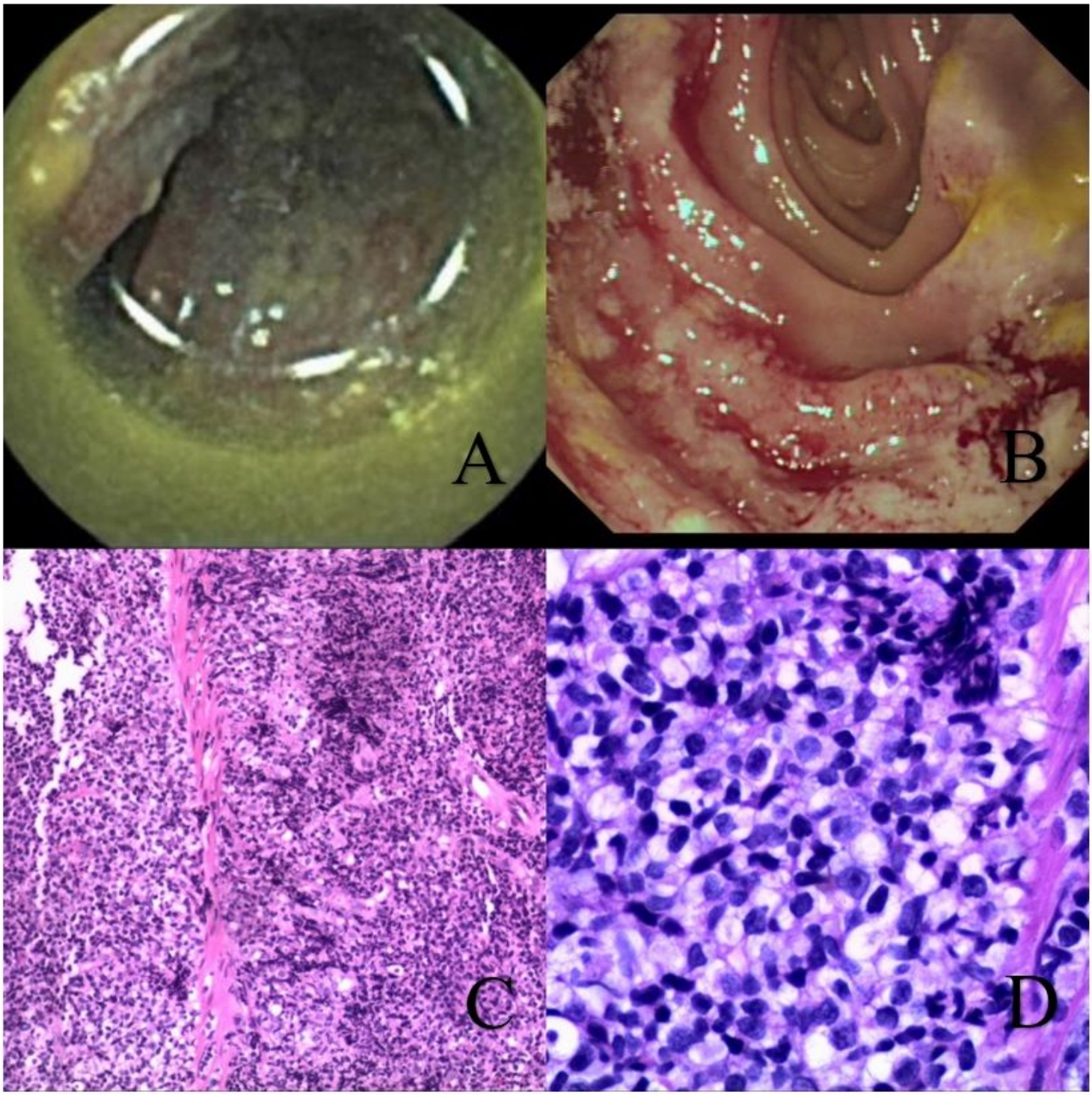

Figure 1

1A: Capsule endoscopy The intestinal preparation was poor, multiple deep basement depressions could be seen in the jejunal mucosa. 1B: Single balloon enteroscopy Large patches of ulcerative lesions were seen in the upper jejunum 1C 1D: Histologic appearance of monomorphic epitheliotropic intestinal T-cell lymphoma The cells were equal, lightly stained cytoplasm, obvious nucleolus, and mitosis. 1C: HE×100 1D: HE×400

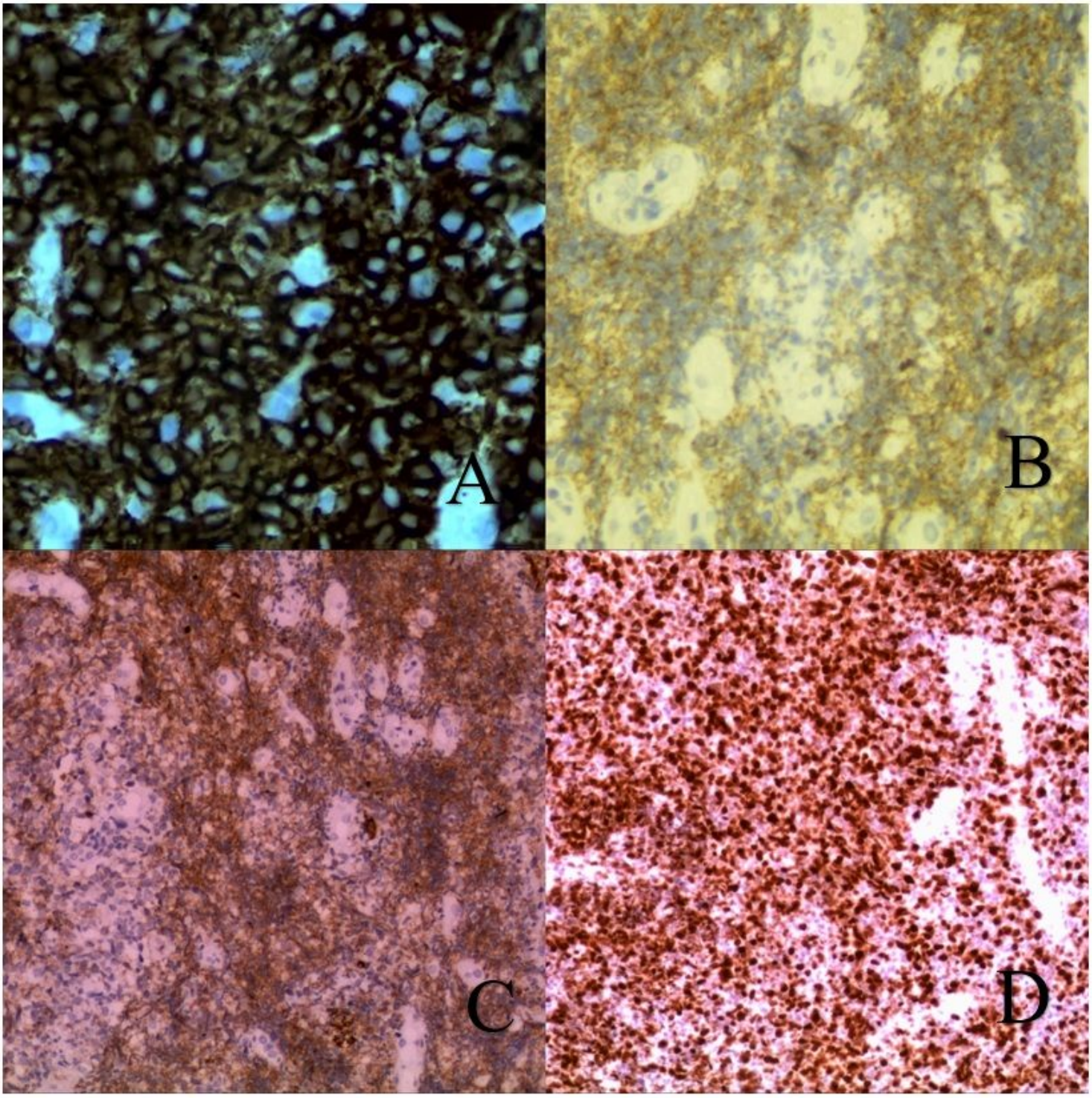

Figure 2

2A: CD3 immunohistochemical staining 2B: CD8 immunohistochemical staining 2C: CD56 immunohistochemical staining 2D: The proliferation index of Ki-67 was 80% immunohistochemical staining

Supplementary Files

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- carechecklist.jpg