Primary Extra Nodal NK/T Cell Lymphoma in the Gallbladder: A Rare Case Report

Ya Jiang

People's Liberation Army Joint Logistic Support Force 920th Hospital

Shi-Yi Long

People's Liberation Army Joint Logistic Support Force 920th Hospital

Wen-Mang Xu

People's Liberation Army Joint Logistic Support Force 920th Hospital

Zi-Ran Gao

People's Liberation Army Joint Logistic Support Force 920th Hospital

Xin-Yan Pan

People's Liberation Army Joint Logistic Support Force 920th Hospital

Qiang Feng

People's Liberation Army Joint Logistic Support Force 920th Hospital

Yuan-Yuan Wang (✉ wyy131328@126.com)

People's Liberation Army Joint Logistic Support Force 920th Hospital <https://orcid.org/0000-0001-9589-2977>

Case Report

Keywords: case report, extra nodal NK/T cell lymphom, gallbladder, CD56, pathology, diagnose

Posted Date: September 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-801081/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Extra nodal NK/T cell lymphoma (ENKTL) is rarely occurred in the gallbladder, and it is generally difficult to diagnose before surgery. Here we present a case of primary ENKTL of gallbladder.

Case presentation A 61-year-old female with pain in the right upper abdomen, and Murphy's sign was positive. Ultrasonography showed that a submucosal tumor-like lesion in the neck of the gallbladder, and the gallbladder wall thickness was 0.6cm; there were several high-signal stone shadows. Microscopic examination revealed coagulative necrosis in the lamina propria of the mucosa, the tumor cells were grown diffusely infiltrating, which with medium to large size and inconspicuous or small nucleoli. Immunohistochemistry showed that the tumor cells were positively expressed CD3, CD2, CD56, CD43, TIA-1, Perforin, Granzyme-B, and EBER-ISH (-). Based on these findings, the pathological diagnosis was ENKTL of the gallbladder. The patient received CHOP chemotherapy regimens, who has been free of recurrence for 8 months after the surgery.

Conclusion In the early stage, histological diagnosis of ENKTL is difficult, and the patient may not have obvious symptoms, for patients with the gallbladder wall thickens and has protrusions, ENKTL should be regarded as one of the differential diagnosis.

Background

Malignant lymphomas of the gallbladder are common, but extra nodal NK/T cell lymphoma (ENKTL) that occurs in the gallbladder is rare. Approximately 80% of ENKTL occur in the nose, nasopharynx, oropharynx, waldeyer ring, and upper aerodigestive tract, these lymphomas are referred to as nasal NK/T cell lymphomas [1 2]. Skin, testes, gastrointestinal tract, soft tissues and salivary glands are also common. In this case, the preoperative ultrasonography (US) showed sub mucosal polypoid lesions, which is an atypical feature of gallbladder carcinoma. Thus, we herein report a case of ENKTL of the gallbladder, aims to broaden the scope of differential diagnosis of gallbladder tumor.

Case Presentation

A 61-year-old female has intermittent pain with no obvious cause in the right upper abdomen three days ago, there was no obvious cause, which radiated to the right shoulder and back, accompanied by nausea and vomiting. The vomit was coffee grounds, no hematemesis or melena. On physical examination, it was found that the skin and mucous membranes of the whole body were yellowish, and the sclera no yellowing, slight tenderness in the right upper abdomen, rebound pain, local muscle tension, and Murphy's sign was positive.

Admission test showed: liver function: alanine aminotransferase (ALT) 237 IU/L, aspartate aminotransferase (AST) 105 IU/L, total protein (TP) 58.3 g/L, total bilirubin (TBIL) 102.8μmol/L, direct bilirubin (DBIL) 73.34μmol/L, alkaline phosphatase (ALP) 489 IU/L, indirect bilirubin (IBIL) 29.5 IU/L, γ-GCT 545 IU/L; Tumor markers: alpha fetoprotein (AFP) < 1.1 unit/L, CA19-9 40.15 U/mL. US indicated a

submucosal tumor-like lesion of the gallbladder (Fig. 1A), acute cholecystitis, gallbladder stones (Fig. 1B), the thickening of the gallbladder wall (0.6 cm) (Fig. 1A), bile duct stones with dilation. There were no obvious abnormalities in the routine examination before surgery. Based on these imaging findings, there was no clear evidence to diagnose the lesion as a malignant tumor. Preoperative diagnosis: Common bile duct stones with acute cholangitis, obstructive jaundice, gallbladder polyp and stones, diabetes.

Since the patient had clear indications for surgery, after admission 3 days, he was underwent laparoscopic cholecystectomy under general anesthesia, choledochectomy, and choledochoscopy. During the operation, it was found that the gallbladder wall was thickened, a 0.8cm protrusion was seen in the gallbladder neck, an extensively adhered was seen between the gallbladder and the transverse colon, and the diameter of the common bile duct was 1.0cm.

Pathological results showed the necrosis was seen in the lamina propria and muscularis of the gallbladder mucosa (Fig. 2A). The blood vessel wall was destroyed by tumor cells, which leads to the injury of vascular war and fibrinoid necrosis (Fig. 2B). The cells size was seen to uniform, the cytoplasm is transparent, and some nuclei are distorted. The mitotic figures were easily to see (Fig. 2C). The immunohistochemistry study demonstrated that the lymphoid cells were positive for CD3 (Fig. 2D-1), CD56 (Fig. <link rid="fig2">2</link>D-2), CD2,CD43, TIA-1, Granzyme B, Perforin, and negative for CD20, CD79a, Pan-CK, Bcl-6, CD10, MUM1 and cyclin-D1, Ki-67 proliferation index was high (approximately 80%). Based on these findings, the final pathological diagnosis was ENKTL of the gallbladder. The patient has undergone adjuvant chemotherapy after surgery, and there has been no recurrence for 8 months.

Discussion And Conclusions

Primary lymphoma of the gallbladder is quite rare and is defined as a disease confined to the gallbladder, with or without involvement of adjacent lymph nodes[3], and there are few reports in the literature. According to the new classification of World Health Organization (WHO) in 2016, B-cell lymphoma is the most common of primary gallbladder lymphoma, such as diffuse large B-cell lymphoma and mucosal-associated lymphoid tissue lymphoma. ENKTL is rarely reported [4]. The current case is only the third case that has occurred in the gallbladder and bile duct [5 6]. Which one case that occurred in the bile duct was found at autopsy. The other case was diagnosed as non-Hodgkin lymph oma after cholecystectomy, bone marrow biopsy results suggest a diagnosis of bone marrow non-Hodgkin's lymphoma, NK/T cell tumor.

ENKTL is a kind of non-Hodgkin lymphoma that originates from mature NK cells and NK-like T cells[7]. It usually occurs in the nasal cavity, nasopharynx, sinuses and palate, but it is also rare in lungs, testes, adrenal glands, etc [8 9]. Those who occur in the nasal cavity have nasal congestion, necrosis of the diseased mucosa and ulcers, and the accessory sinuses are involved. Skin lesions are manifested as nodules and often accompanied by ulcers. Perforations are common in those who occur in the intestines.

Some cases may be associated with hematopoietic syndrome. This patient presented with pain in the upper abdomen, nausea, and vomiting. No masses in the nasal cavity and other parts.

The pathogenesis of ENKTL is not fully understood. At present, it is found to be closely related to Epstein-Barr virus (EBV) infection, especially in nasal cases, EBV infection is present at 80–100% [10], while the detection rate of EBV in other non-nasal parts is relatively low (15–50%). Some previous studies have shown that, compared with CD56 + EBV⁺ lymphoma, CD56 + EBV⁻ lymphoma at external nasal sites is a less aggressive malignant tumor and shows less necrosis [11]. Moreover, they propose that ENKTL at extra nasal sites should be diagnosed based on EBV infection status, cytotoxic T or NK phenotype, and not related to genotype. In our case, the patient's EBER is negative, which may indicate a better prognosis.

Morphologically, 1) necrosis is common in the mucosa, with diffuse infiltration of tumor cells; 2) destruction of blood vessel walls and fibrinoid necrosis are common; 3) accompanied by infiltration of various inflammatory cells, such as lymphocytes, eosinophils, tissue cells, and plasma cells Iso-reactive inflammatory cells infiltrate; 4) tumor cells have various morphologies, irregular or long nuclei, granular chromatin, inconspicuous nucleoli or small nucleoli, light to translucent cytoplasm, and mitotic figures are easy to see. Immunohistochemistry shows the tumor cells positively expressed CD3, CD56, CD43, CD2, TIA-1, Granzyme B, Perforin, negative in CD20, CD79a and other about B-cell-related antigens [6]. In the current case, our findings were consistent with the histological form of this disease.

Primary ENKTL of the gallbladder is rare, so it needs to be distinguished from inflammatory lesions or other lymphomas. Inflammatory lesions usually lack of a clonal marker for NK-cells (CD56). Other lymphomas can usually be distinguished based on immune markers. T-cell lymphomas are usually positive for T cell markers and TCR rearrangement; B-cell lymphomas are usually B-cell markers positive and IgH gene rearrangement.

Nasal NK/T cell lymphoma is sensitive to radiotherapy, but often insensitive to chemotherapy, or relapse quickly after a short remission. It is currently believed that combined radiotherapy and chemotherapy is the best choice for the treatment of this type of lymphoma [12]. Our patient received 4 cycles of CHOP since he was diagnosed with ENKTL. Now with no recurrence, and we will continue to follow up.

In conclusion, we present a case with primary ENKTL with gallbladder. The incidence of such condition is extremely low but has significant clinical value. This case broadens the scope of differential diagnosis of gallbladder lymphoma. After all, most of the lymphomas currently reported in the gallbladder are B-cell lymphomas. After the diagnosis of ENKTL, it is necessary to fully understand the patient's medical history to rule out nasal metastasis. At the same time, the negative EBV in this case may also be related to a good prognosis.

Abbreviations

Extra nodal NK/T cell lymphoma: ENKTL

Ultrasonography: US

Alanine aminotransferase: ALT

Aspartate aminotransferase: AST

Total protein: TP

Total bilirubin: TBIL

Direct bilirubin: DBIL

Alkaline phosphatase: ALP

Indirect bilirubin: IBIL

Alpha fetoprotein: AFP

Epstein-Barr virus: EBV

World Health Organization: WHO

Declarations

Conflicts of interest

The authors have declared no conflicts of interest.

Acknowledgements

This work was supported by the grants from the Application Fundamental Research Program Growth Project of 920th Hospital (2019YGB01).

Author contributions

Ya Jiang was responsible for the original draft, the submission and the revise of the manuscript, Shi-Yi Long was responsible for collect the data, and revise of the manuscript, Wen-Mang Xu and Zi-Ran Gao contributed to pathological diagnosis, and postoperative follow-up investigation, Xin-Yan Pan and Qiang Feng were responsible for immunohistochemistry and In situ hybridization, Yuan-Yuan Wang was responsible for collecting data and guiding the project.

Statement

Informed consent was obtained from the patient for being included in the study.

References

1. Tse E, Kwong YL. The diagnosis and management of NK/T-cell lymphomas. *Journal of hematology & oncology* 2017;10:85.
2. Tse E, Kwong YL. How I treat NK/T-cell lymphomas. *Blood* 2013;121:4997-5005.
3. Pezzuto R, Di Mauro D, Bonomo L, Patel A, Ricciardi E, Attanasio A, Manzelli A. An Unusual Case of Primary Extranodal Lymphoma of the Gallbladder. *Hematology reports* 2017;9:6972.
4. Mani H, Climent F, Colomo L, Pittaluga S, Raffeld M, Jaffe ES. Gall bladder and extrahepatic bile duct lymphomas: clinicopathological observations and biological implications. *The American journal of surgical pathology* 2010;34:1277-86.
5. Gao F, Zhao H, Chen X, Dong X, Liu T, Fu X. Gallbladder non-Hodgkin's lymphoma: Case report. *International journal of surgery case reports* 2019;61:218-21.
6. Ito H, Hiraiwa SI, Sugiyama T, et al. An autopsy case of primary extranodal NK/T cell lymphoma (extranodal NK/T-cell lymphoma) of the bile duct. *Clinical journal of gastroenterology* 2019;12:209-12.
7. Kwong YL. The diagnosis and management of extranodal NK/T-cell lymphoma, nasal-type and aggressive NK-cell leukemia. *Journal of clinical and experimental hematopathology : JCEH* 2011;51:21-8.
8. Tababi S, Kharrat S, Sellami M, Mamy J, Zainine R, Beltaief N, Sahtout S, Besbes G. Extranodal NK/T-cell lymphoma, nasal type: report of 15 cases. *European annals of otorhinolaryngology, head and neck diseases* 2012;129:141-7.
9. Jiménez-Pérez JC, Yoon MK. Natural Killer T-Cell Lymphoma of the Orbit: An Evidence-Based Approach. *Seminars in ophthalmology* 2017;32:116-24.
10. Kuo TT, Shih LY, Tsang NM. Nasal NK/T cell lymphoma in Taiwan: a clinicopathologic study of 22 cases, with analysis of histologic subtypes, Epstein-Barr virus LMP-1 gene association, and treatment modalities. *International journal of surgical pathology* 2004;12:375-87.
11. Ko YH, Cho EY, Kim JE, et al. NK and NK-like T-cell lymphoma in extranasal sites: a comparative clinicopathological study according to site and EBV status. *Histopathology* 2004;44:480-9.
12. Yang Y, Zhu Y, Cao JZ, et al. Risk-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma: analysis from a multicenter study. *Blood* 2015;126:1424-32; quiz 517.

Figures

Figure 1

US test, (A) showing the thickening of the gallbladder wall (yellow arrows), (black arrows) indicates a submucosal tumour-like lesion of in the neck of the gallbladder. (B) showing the gallbladder stones.

Figure 2

(A) Microphotograph showing mucosal loss, necrosis of mucosa and lamina propria, the tumor cells infiltrated into the serosal layer. (B) The tumor cells destroy blood vessels, leading to the injury of vascular wall and fibrinoid necrosis. (C) The cells size were relatively uniform, the cytoplasm is

transparent, and some nuclei are distorted. The mitotic figures were easily to see (red arrow). (D)
Immunohistochemistry is positive for CD56 (1) and CD3 (2).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CAREchecklistEnglish2013.pdf](#)