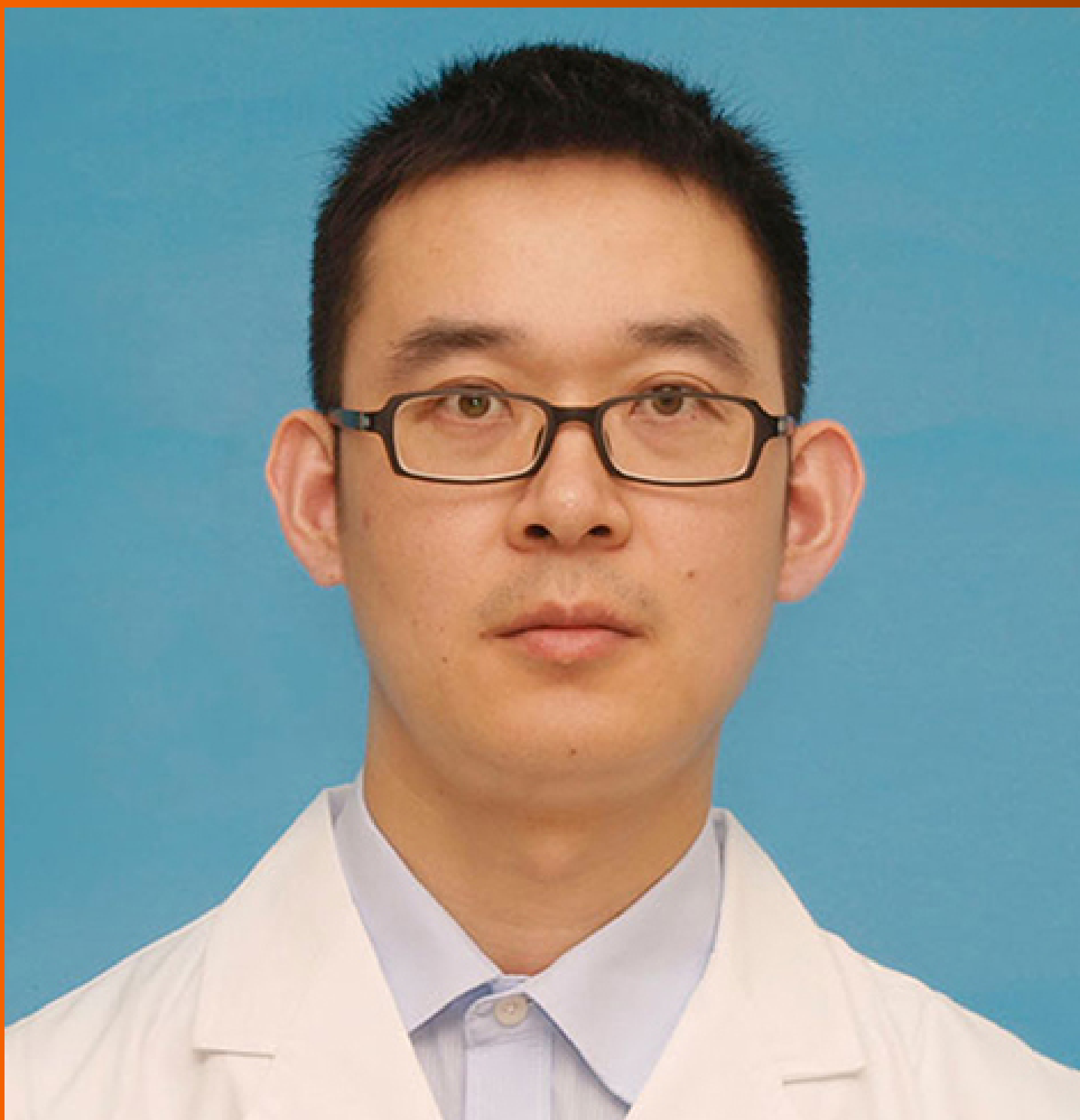


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ABOUT COVER

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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

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Intestinal natural killer/T-cell lymphoma presenting as a pancreatic head space-occupying lesion: A case report

Ya-Nan Wang, Yi-Miao Zhu, Xiao-Ju Lei, Yuan Chen, Wan-Mao Ni, Zheng-Wei Fu, Wen-Sheng Pan

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Abstract

BACKGROUND

Intestinal natural killer/T-cell lymphoma (NKTCL) is a rare and aggressive non-Hodgkin's lymphoma, and its occurrence is closely related to Epstein-Barr virus infection. In addition, the clinical symptoms of NKTCL are not obvious, and the specific pathogenesis is still uncertain. While NKTCL may occur in any segment of the intestinal tract, its distinct location in the periampullary region, which leads clinicians to consider mimics of a pancreatic head mass, should also be addressed. Therefore, there remain huge challenges in the diagnosis and treatment of intestinal NKTCL.

CASE SUMMARY

In this case, we introduce a male who presented to the clinic with edema of both lower limbs, accompanied by diarrhea, and abdominal pain. Endoscopic ultra-

sound (EUS) showed well-defined homogeneous hypoechoic lesions with abundant blood flow signals and compression signs in the head of the pancreas. Under the guidance of EUS- fine needle biopsy (FNB) with 19 gauge or 22 gauge needles, combined with multicolor flow cytometry immunophenotyping (MFCI) helped us diagnose NKTCL. During treatments, the patient was prescribed the steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide chemotherapy regimen. Unfortunately, he died of leukopenia and severe septic shock in a local hospital.

CONCLUSION

Clinicians should enhance their understanding of NKTCL. Some key factors, including EUS characteristics, the right choice of FNB needle, and combination with MFCI, are crucial for improving the diagnostic rate and reducing the misdiagnosis rate.

Key Words: Intestinal natural killer/T-cell lymphoma; Endoscopic ultrasound-guided fine-needle biopsy; Multicolor flow cytometry immunophenotyping; Diagnosis; Case report

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Core Tip: Intestinal natural killer/T-cell lymphoma (NKTCL) is a rare form of lymphoma with a low diagnosis rate. The patient presented in this case was eventually diagnosed with intestinal NKTCL. The patient initially improved after receiving chemotherapy with the steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide regimen but died two days after being discharged from the hospital. This case tells us that endoscopic ultrasound may be very helpful in the diagnosis of NKTCL. A 19 gauge or 22 gauge fine needle biopsy needle combined with multicolor flow cytometry immunophenotyping may be a good choice for diagnosing and subtyping lymphoma.

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INTRODUCTION

Intestinal natural killer/T-cell lymphoma (NKTCL) is a rare and aggressive lymphoma[1]. NKTCL accounts for approximately 8%-15% of all gastrointestinal (GI) lymphomas[2]. Today, Asian populations are more likely to develop Epstein-Barr virus (EBV)-associated subtypes of non-Hodgkin's lymphoma, a situation that appears to be related to geographic location[3]. Presently, conventional colonoscopy biopsy has difficulty obtaining a deep enough depth to diagnose the tissue, and the diagnostic rate is low. Here, we present the case of a 44-year-old male patient who presented clinically with edema of both lower limbs associated with diarrhea and abdominal pain. Under the guidance of endoscopic ultrasound (EUS), fine needle biopsy (FNB) with 19 gauge (19 G) or 22 gauge (22 G) needles combined with multicolor flow cytometry immunophenotyping (MFCI) may play a decisive role in the final diagnosis of intestinal NKTCL.

CASE PRESENTATION

Chief complaints

A 44-year-old Chinese male was admitted to the hospital with persistent diarrhea, abdominal pain, lower limb edema and weight loss for more than one year that had been aggravated for one month.

History of present illness

The patient had loose yellow stools 4 to 5 times a day, and the stool weighed more than 500 g total, without bloody stools or melena. He suffered from this condition and lower limb edema for one year while also experiencing periumbilical abdominal pain, which was moderately paroxysmal colic pain. The patient visited several hospitals and was diagnosed with possible "protein-losing enteropathy" according to "hypoproteinemia" in laboratory tests and "edema and thickening of the small bowel wall"

on contrast-enhanced computed tomography (CT). However, the gastrointestinal endoscopy reported a normal view. Probiotics, antibiotics, and digestive enzymes were prescribed to the patient, but his symptoms did not improve. One month before admission, symptoms of abdominal distention, mild abdominal pain in the right upper quadrant, and obvious weight loss (8 kg one month) had developed, without fever or jaundice.

History of past illness

The patient reported no remarkable history of past illness.

Personal and family history

The patient drank 500 mL of alcohol and smoked 10 cigarettes a day for 30 years. He reported no remarkable family history.

Physical examination

On physical examination, the patient's vital signs were stable, with a body temperature of 36.8 °C on admission. No pale or jaundice was observed, and there was no superficial lymphadenopathy. A mass of approximately 4 cm in diameter was palpable in the right part of the distend abdomen. Shifting dullness was positive upon examination. There was no tenderness, no abnormal bowel sounds or rate, and no palpable hepatosplenomegaly or Murphy's sign. Moderate symmetric edema of both lower limbs was observed.

Laboratory examinations

Laboratory findings on admission indicated mild anemia (hemoglobin, 116 g/L) and hypoproteinemia (albumin, 18.5 g/L). Liver function was mildly elevated (alkaline phosphatase, 290 U/L; gamma-glutamyl transpeptidase (γ -GT) 87 U/L). Leukocyte, platelet, bilirubin, lactate dehydrogenase (LDH), thyroid function and serum tumor markers were within normal limits, except elevated carbohydrate antigen 125 (517 U/mL). Tests for autoantibody, stool culture, antibody against tuberculosis, cytomegalovirus immunoglobulin M antibody, EBV DNA, and Clostridium difficile toxin detection were negative. In addition, the vitamin B3 Level was 17.1 ng/mL, which was within the normal range. The reticulocyte count was $45.50 \times 10^9/L$, and the reticulocyte ratio was 1.12%, and these results were negative. The total bilirubin level was 12.0 $\mu\text{mol/L}$, the direct bilirubin level was 4.9 $\mu\text{mol/L}$, the indirect bilirubin level was 7.1 $\mu\text{mol/L}$, the creatinine level was 63.1 $\mu\text{mol/L}$, and the glomerular filtration rate was 134.76 mL/min/1.73 m², which were all within the normal range.

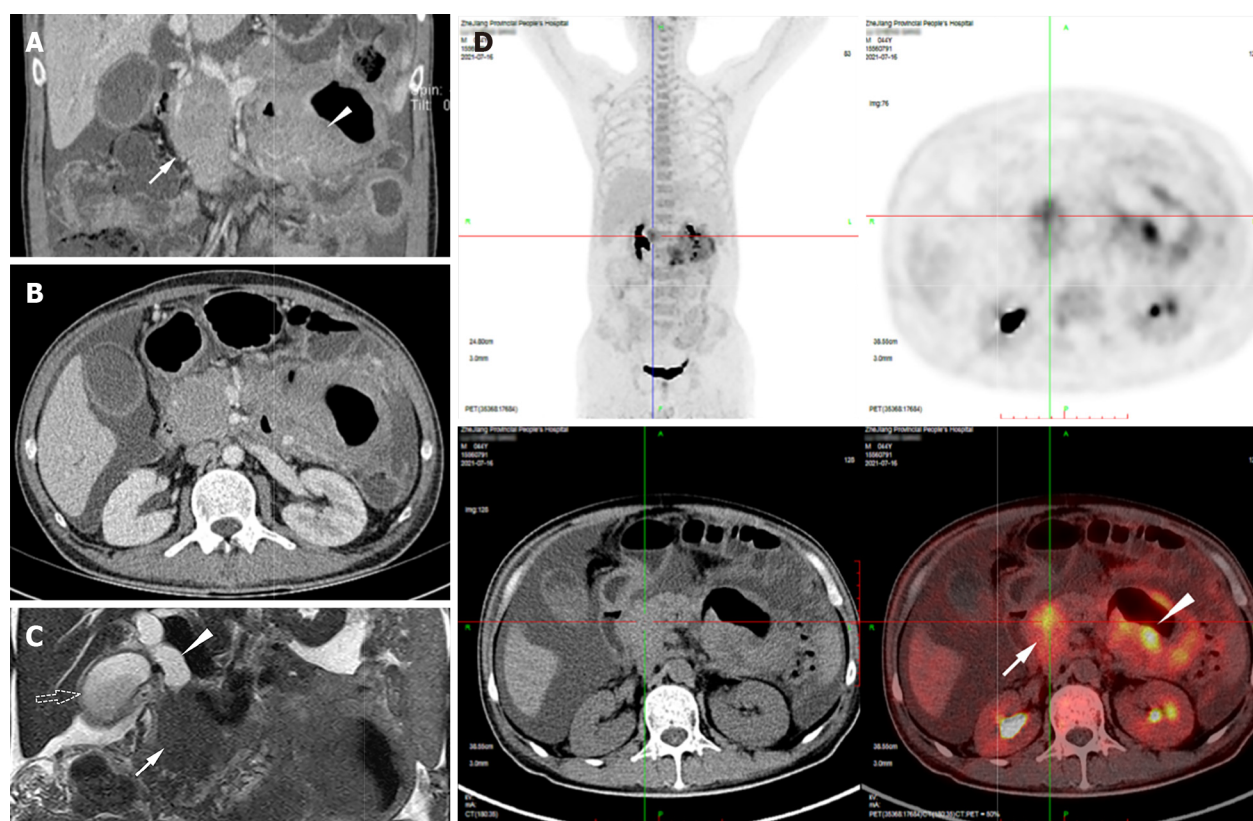
A diagnostic paracentesis was performed, which revealed bloody ascites with increased red blood cells (81500), nucleated cells (657), and protein concentrations (1790 mg/dL). The adenosine deaminase, amylase, LDH, and carcinoembryonic antigen levels in ascites were normal. The smear for acid-fast bacilli and exfoliative cytology were negative.

Imaging examinations

Esophagogastroduodenoscopy in a previous hospital revealed chronic gastritis, while colonoscopy found several small polyps, which were confirmed as tubular adenomas according to pathology. Capsule endoscopy showed segmental hyperemia, edema, and partial atrophy of villi in the jejunum. On the computed tomography enterograph, there was a circular, solid-occupying lesion in the pancreatic head that was 88 mm \times 47 mm \times 52 mm in size. The jejunal wall was thickened to 34 mm but did not cause intestinal stenosis or obstructive signs. These two lesions had uniform CT density and moderate enhancement (Figure 1A and B). Magnetic resonance (MR) cholangiopancreatography revealed that the pancreatic head mass, together with the biliary duct, was dilated to 18 mm and the gallbladder was enlarged (Figure 1C). 18F-Fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT) detected intense FDG uptake within the pancreatic head lesion and jejunal wall thickening (SUVmax = 7.2 and SUVmax = 10.3, respectively) (Figure 1D).

FURTHER DIAGNOSTIC WORK-UP

During hospitalization, the patient developed a high fever of 38.8 °C and jaundice. The direct bilirubin level increased to 110.3 $\mu\text{mol/L}$, ALP 432 U/L, and γ -GT 281 U/L. We administered moxifloxacin as an anti-infective treatment and performed EUS-FNB for further diagnosis. EUS (OLYMPUS EUS EU-ME2, GIF-UCT260, Olympus Corporation, Tokyo, Japan) revealed a 51.0 mm \times 45.8 mm well-defined homogeneously hypoechoic lesion in the pancreatic head region. Color and power Doppler ultrasound showed hypervascularity. The pancreatic head parenchyma was adjacent to the mass, but the boundaries were preserved. The main pancreatic duct ran behind the lesion naturally, without any signs of infiltration or dilatation (Figure 2).



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Figure 1 Radiology findings of the lesions. A: There was circular solid occupying lesion in pancreatic head with 88 mm × 47 mm × 52 mm in size (white arrow). Jejunal wall thickened to 34 mm (white arrow head), without intestinal stenosis and obstructive signs; B: These two lesions were both in uniform computed tomography (CT) density and moderate enhancement; C: Magnetic resonance cholangiopancreatography revealed the head pancreatic mass (white arrow) with dilated biliary duct (white arrow head) and enlarged gallbladder (dotted arrow); D: 18F-Fluorodeoxyglucose(18-F FDG) positron emission tomography/CT detected intensive FDG uptake within the pancreatic head lesion (white arrow) and the jejunal wall thickening (white arrow head).

FINAL DIAGNOSIS

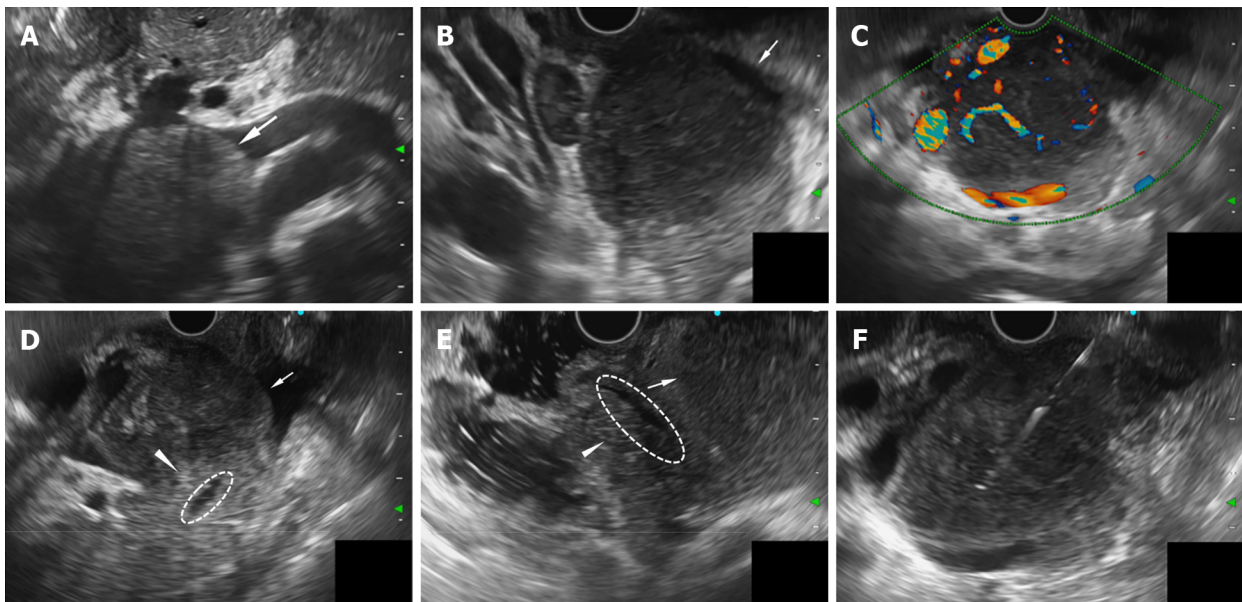
A 22 G needle (EchoTip ProCore®, Cook Medical, Limerick, Ireland) was applied for FNB using a transpyloric approach, with suction applied using a 20 mL syringe (Figure 2F). Biopsy specimens were partially fixed in formalin, and embedded in paraffin for pathology and partially preserved in saline solution for MFCI. Microscopic examination revealed small round cells arranged in diffuse sheets. On immunohistochemistry, the cells were positive for CD3, CD56, CD45RO, and CD8 and were scattered positive for T-cell intracellular antigen and granzyme B. CD20, chromogranin A, synaptophysin, and Epstein-Barr virus-encoded RNA were negatively expressed in the tumor cells. The Ki-67 proliferation index was 80% (Figure 3).

In MFCI, a predominantly heterotypic (90.953%) NK lymphocyte cell population was identified. These cells were TRBC1-, CD5-, TCRγδ-, CD2++, CD3++, CD4-, CD8+, CD56++, CD25-, CD5-, CD99++, TCRαβ-, CD335-, CD28-, and CD57-. CD158a, h expression in abnormal NK cells was 40.123% (Figure 4).

Based on the above findings and advice from consulted hematologists, we proposed a diagnosis of intestinal NKTCL with retroperitoneal lymph node involvement (pancreatic head lesion).

TREATMENT

Endoscopic retrograde cholangiopancreatography was performed for biliary drainage with fully covered self-expanding metal stents inserted into the common bile duct to relieve biliary obstruction. The patient's temperature and jaundice gradually stabilized. Subsequently, he was transferred to the hematology department. Further bone marrow (BM) biopsy and flow cytometry indicated that no heterotypic NK lymphocytes were observed, and the NK cells in BM were in a normal proportion as well as phenotype. Therefore, the patient was prescribed the SMILE chemotherapy regimen.



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Figure 2 Endoscopic ultrasound characteristic of the lesion located in pancreatic head region. A and B: A 51.0 mm × 45.8 mm well-defined homogeneously hypoechoic lesion located in the pancreatic head region (A: Transgastric observation, white arrow; B: Transduodenal observation, white arrow); C: The lesion is hypervascularity in color and power Doppler ultrasound; D and E: Observing in the duodenal bulb (D) and descending part of duodenum (E), the lesion (white arrow) is adjacent to the pancreatic head parenchyma (white arrow head), but boundaries were still preserved. The main pancreatic duct (dotted circle) ran alongside the lesion naturally, without any signs of infiltration or dilatation; F: Endoscopic ultrasound-Fine needle biopsy using a 22 gauge needle was performed.

OUTCOME AND FOLLOW-UP

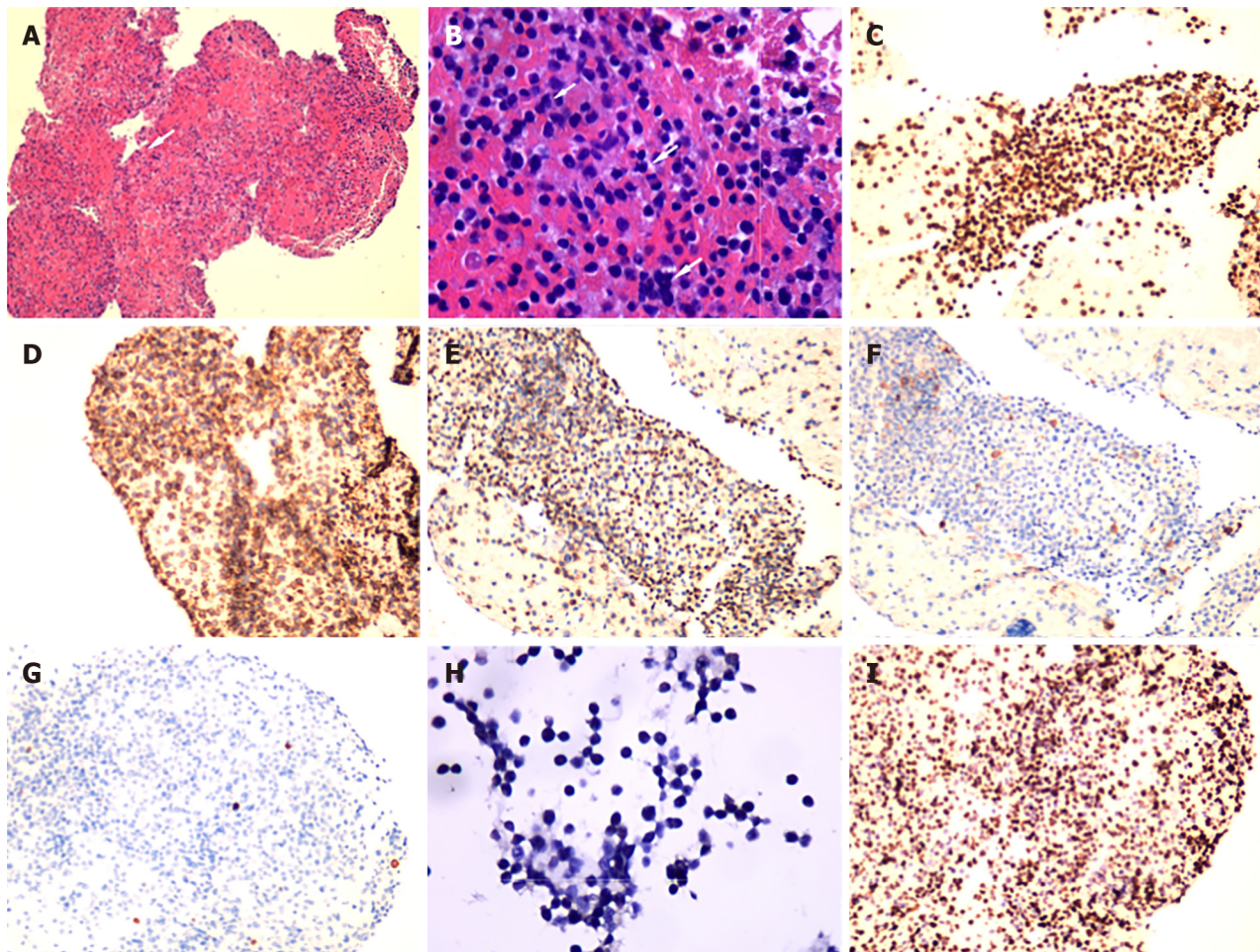
The first SMILE regimen was performed from August 1, 2021 to August 4, 2021. On the first day of chemotherapy, the patient had diarrhea and developed hematochezia once, approximately 50 g. However, the symptoms of diarrhea, abdominal pain, and hematochezia were relieved on the second day of chemotherapy. The patients stayed in the hospital until August 10, 2021, when he improved uneventfully without leukocytopenia (white blood cell count, $5.05 \times 10^9/L$). Unfortunately, two days after discharge, he died from leukopenia and severe septic shock in a local hospital.

DISCUSSION

We introduced a case of intestinal NKTCL with retroperitoneal lymph node involvement, presenting as a pancreatic head space-occupying lesion. The patient was efficiently diagnosed through EUS-FNB combined with multicolor flow cytometry immunophenotyping.

Intestinal NKTCL, as a category of extranodal lymphoma, has a low incidence, accounting for approximately 8%-15% of GI lymphomas, but has a poor prognosis[2,4]. Intestinal NKTCL is mostly associated with EBV infection, and its incidence is characterized by distinct ethnic groups and regional distributions; it is more prevalent in the East and in South America, but with a low overall incidence[5]. Abdominal lymphoma is often encountered in clinical practice, while primary pancreatic lymphoma (PPL) only accounts for 0.1% of malignant tumors[6,7]. Due to the nonspecific clinical symptoms and endoscopic findings, as well as the high negative rate of mucosal biopsy, it is difficult to distinguish intestinal NKTCL from inflammatory disease or malignant tumors of the pancreas, hepatobiliary tissue and other organs. For NKTCL, its diagnosis and prognosis have always been less satisfactory[8]. In a retrospective study published in 2014, the authors suggested that the average time required for a correct diagnosis was 12.8 mo. They noted that inflammatory cell infiltration is the most common factor that delays the diagnosis of NKTCL[9].

In the differential diagnosis process of NKTCL, PET-CT can not only provide standard images but also help accurately stage the disease[10-12]. At the same time, the accuracy of MR is also relatively high [13]. A study of 36 patients with nasal-type NKTCL reported that the accuracy of PET-CT *vs* MR was 99% *vs* 92.7%, respectively. However, the sensitivity of PET-CT compared with MR was 100% *vs* 81.4%, respectively, and MR examination of 16 lesions showed 11 negative results[14]. With high resolution, EUS mainly provides real-time imaging and texture of the target object, providing a more detailed description of lesion characteristics and the relationship with the surrounding organs. To our knowledge, there is no literature summary about the EUS characteristics of NKTCL. According to our case and experience, the EUS features of lymphoma, as a mesenchymal tumor, are summarized as



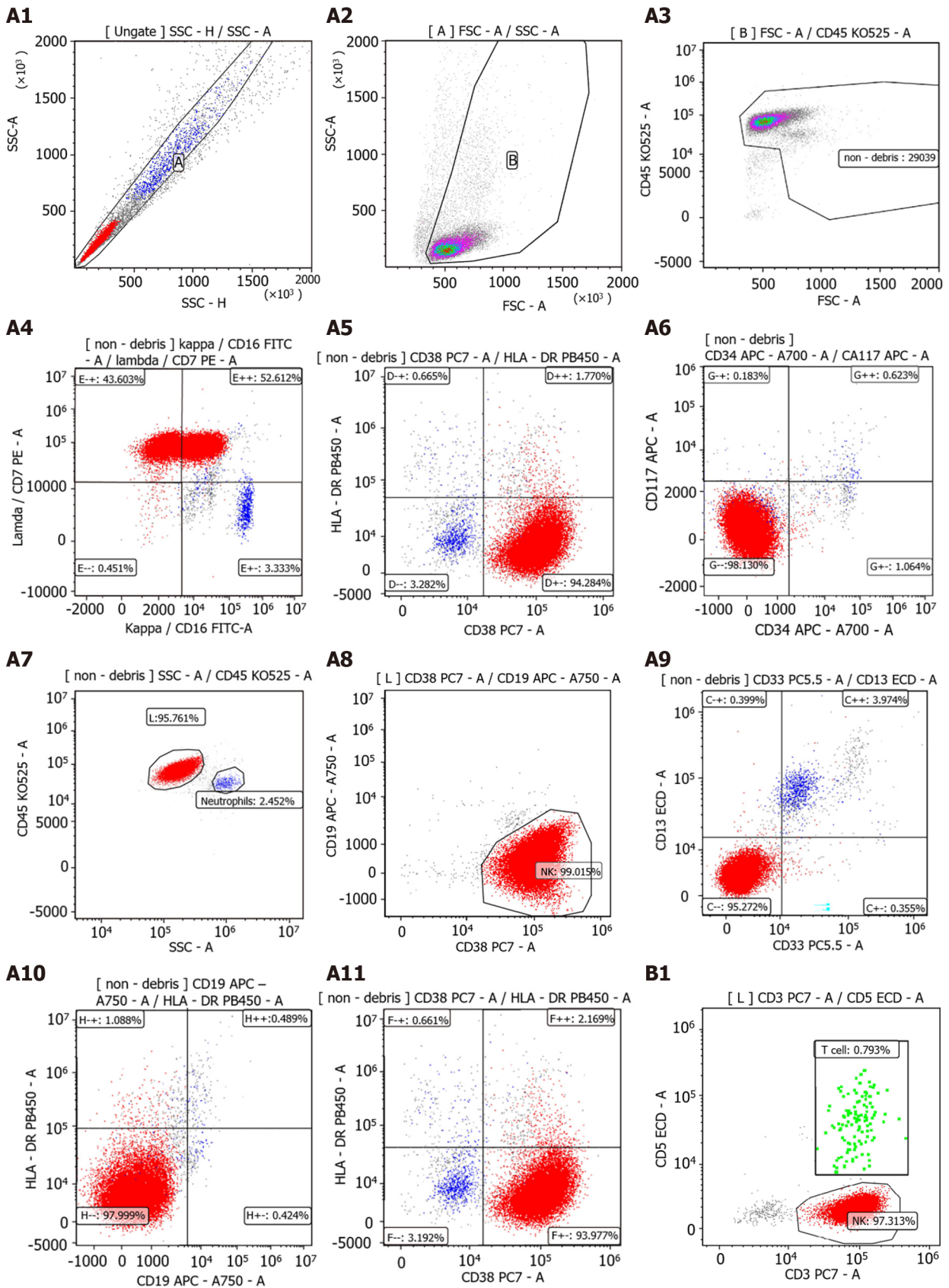
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Figure 3 Pathological findings in Hematoxylin and Eosin staining and Immunohistochemical results. A and B: Microscopic examination revealed small round cells (A: 100 ×, white arrow) arranged in diffuse sheets, with nuclear membrane irregularity (B: 600 ×, white arrow); C-I: Immunohistochemical results revealed that the expression of cluster of differentiation (CD) 3, CD8 and CD56 was positive. The expression of CD20, CD4 and EBER was negative, and Ki-67 was approximately 80%.

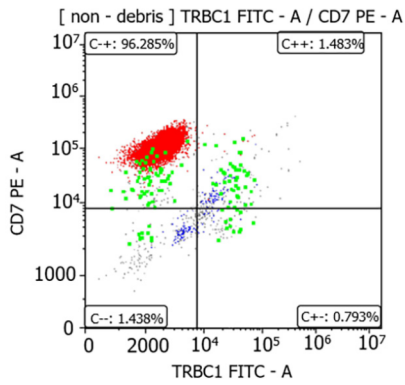
follows: it has well-defined borders, homogeneous internal echogenicity, and abundant blood flow signal lesions with a relatively large diameter. Even in large lesions, manifestations of compression and pushing are commonly be found, without signs of the invasion of blood vessels, bile ducts, pancreatic ducts, or parenchyma of surrounding organs, which are common in epithelial carcinoma.

In the case of suspected lymphoma, FNB should be applied in addition to the immunohistochemistry analysis for not only diagnosis but also subtyping. In a report of 240 patients with lymphoma, needle sizes of 19 G and 22 G were used. For the most part, the choice of the conventional 19 G needle was valid; however, it was ineffective in two patients with periduodenal lesions[15]. The results of a multicenter study of 109 patients with solid lesions indicated that the use of 19 G ProCore™ needles achieved a pathology assessment rate of 89% and an accuracy of 86% for solid lesions[16]. With the use of a small-gauge needle such as 22 G, the lymphoma subtyping rate of cases may range from 66.6% to 87.5% [15]. MFCI plays an integral role in the screening and diagnosis of lymphoma. In some cases, especially when observing relatively clear space-occupying lesions is difficult, MFCI is indispensable [17]. In this case, we used MFCI to help us make a correct diagnosis. A recent study showed that only 28% of patients were diagnosed with lymphoma, compared with 91% of patients with pancreatic adenocarcinoma. However, when MFCI was added, the diagnostic rate of primary PPL increased to 100% [18]. Presently, in the course of NKTCL treatment, asparaginase-containing chemotherapeutic schemes are the standard treatment regimen[19]. Based on previous experience, SMILE is the most popular regimen for the treatment of NKTCL[20]. In a study of 87 NKTCL patients treated with the SMILE regimen, for newly diagnosed stage III/IV patients, the complete response rate was 40%-54%, and the 5-year overall survival rate was 47% [21].

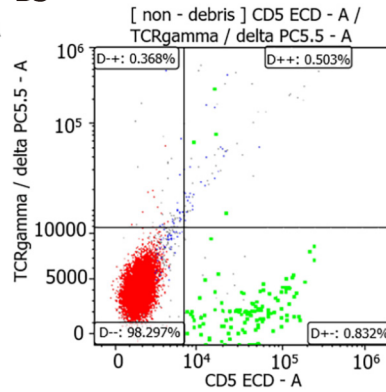
In this case, the patient presented with persistent diarrhea, abdominal pain, edema of the lower limbs, and weight loss. EUS showed a clear boundary, homogeneous internal echo, abundant blood flow signal lesions and compression signs. Intestinal NKTCL is a rare disease with a poor prognosis and high mortality. In light of the lack of understanding of the disease, diagnosis and treatment are particularly



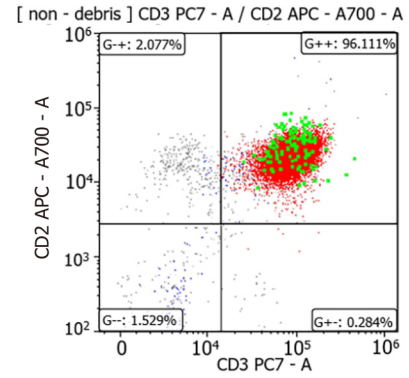
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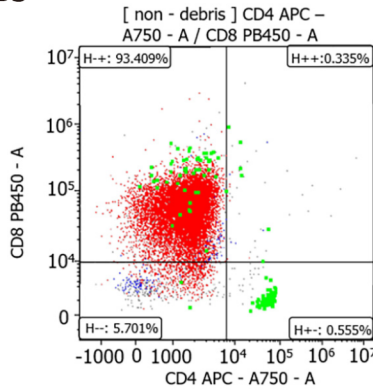
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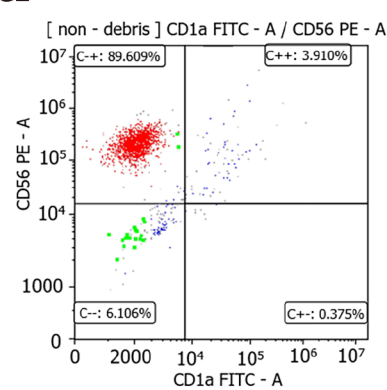
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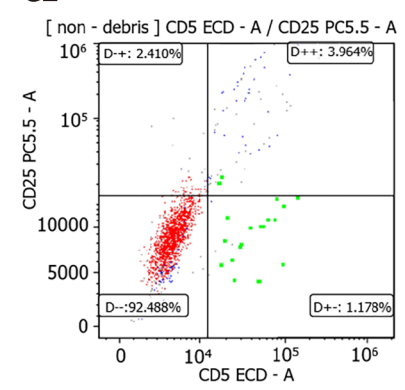
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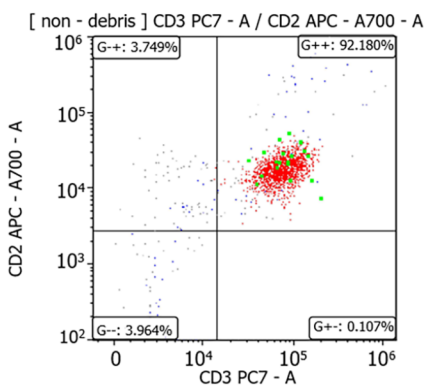
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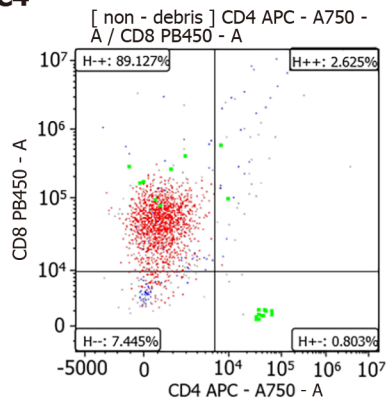
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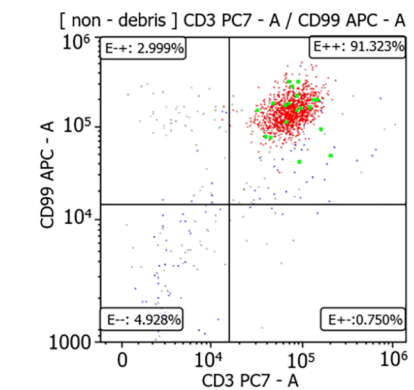
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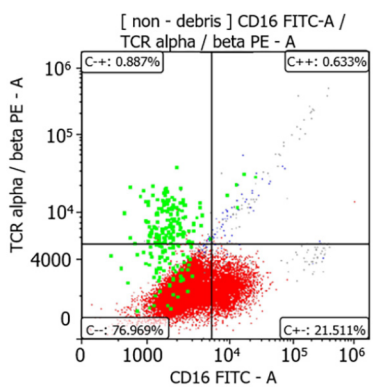
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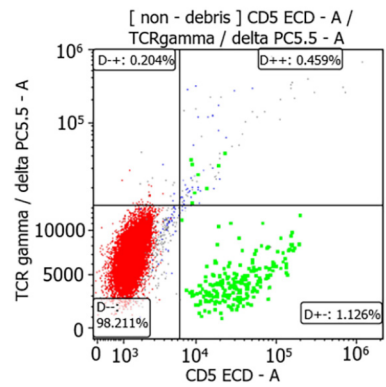
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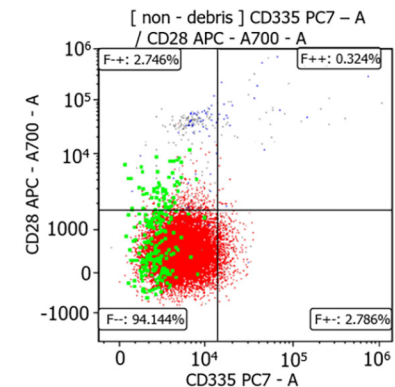
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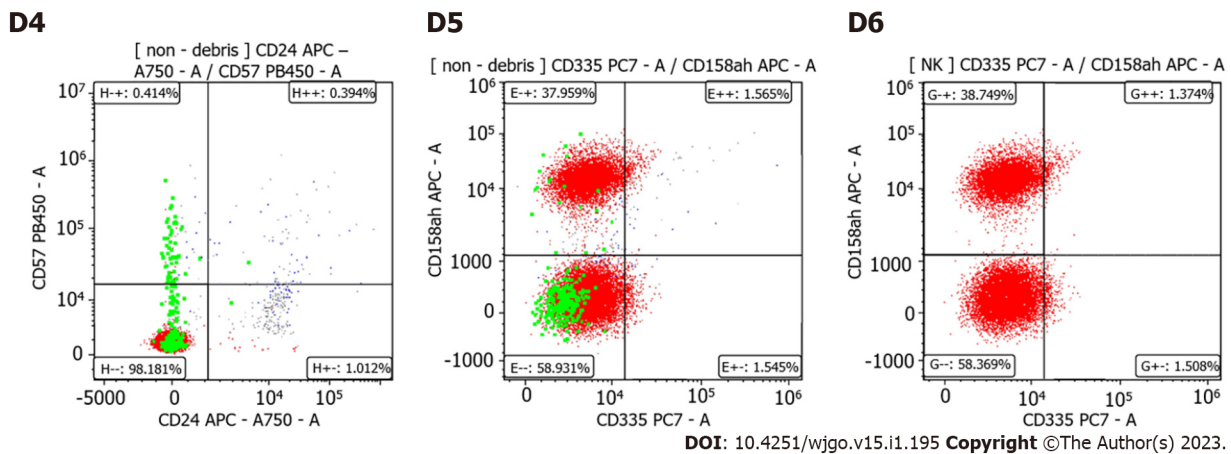


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D3





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Figure 4 Multicolor flow cytometry immunophenotype of the lesion. A: Doublets were excluded by side-scatter height (SSC-H) / side-scatter area (SSC-A) scatter. Debris were excluded by side-Forward-scatter area (FSC-A)/SSC-A and FSC-A/CD45. Abnormal natural kill (NK) cells (red) were gated by SSC-A/CD45 and CD38/CD19. These cells were CD45⁺⁺, CD16 partial positive, CD7⁺⁺, CD38⁺, HLA-DR⁻, CD34⁻, CD117⁻, CD19⁻, CD33⁻, CD13⁻. Neutrophils (blue) were shown as internal control; B-D: The abnormal NK cells (red) were targeting T cell receptor beta-chain constant region 1 (TRBC1)⁻, CD5⁻, TCR gammadelta (TCRγδ)⁻, CD2⁺⁺, CD3⁺⁺, CD4⁻, CD8⁺, CD56⁺⁺, CD25⁻, CD5⁻, CD99⁺⁺, TCRalpha (TCRα)⁻, CD335⁻, CD28⁻, CD57⁻. CD158a, h expression of these cells was 40.123%. Normal T cells (green) were shown as internal control.

crucial. In this case, the combination of EUS-FNB and MFCI played a key role in the diagnosis of intestinal NKTCL.

CONCLUSION

We report a case of intestinal NKTCL presenting as a pancreatic head space-occupying lesion. The summarized EUS characteristics, including well-defined borders, homogeneous internal echogenicity, abundant blood flow signal lesions, and compression signs, might be helpful in differential diagnosis. EUS-FNB with a 19 G or 22 G biopsy needle combined with MFCI could be a good choice for diagnosis and for subtyping lymphoma.

FOOTNOTES

Author contributions: Wang YN, Zhu YM, Lei XJ and Chen Y assembled, analyzed, and interpreted the patient's data and case presentation; Wang YN, Zhu YM, Ni WM and Fu ZW prepared the original manuscript; Pan WS edited and critically revised the manuscript; all authors contributed to writing the manuscript, read and approved the final manuscript.

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