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Diagnostic value of IL-22, IL-23, and IL-17 for NK/T cell lymphoma

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ABSTRACT

NK/T cell lymphoma (NKTCL) is a common blood cancer, and early diagnosis of this disease is crucial. This study is aimed to investigate the roles of IL-17, IL-22 as well as IL-23 for the diagnosis of NKTCL. Sixty-five patients with NKTCL were included and the blood samples were collected, and sixty healthy objectives served as the controls. Serums of the patients and controls were collected. The expression levels of IL-17, IL-22, and IL-23 were examined using enzyme-linked immunosorbent (ELISA) assay. The receiver operator characteristic (ROC) curve was drawn for determining the potential diagnostic value of these cytokines. The serum levels of IL-17 (156.0 ± 67.75 pg/mL), IL-22 (39.98 ± 23.88 pg/mL), and IL-23 (43.05 ± 25.69 pg/mL) were all markedly increased in NKTCL patients (P<0.001); ROC analysis showed the serum level of IL-17, IL-22, and IL-23 could serve as the potential diagnostic biomarker for NKTCL with high sensitivity and specificity. The AUC of IL-17 was 0.9487 (95% confidence interval (CI), 0.9052 to 0.9922). Area under the curve (AUC) of IL-22 was 0.7321 (95% CI, 0.6449 to 0.8192). The AUC of IL-23 was 0.7885 (95% CI, 0.7070 to 0.8699). Our data indicated that IL-17, IL-22, and IL-23 were all increased in NKTCL and may function as potential diagnostic biomarkers for NKTCL.

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Introduction

Extranodal nasal NK/T-cell lymphoma (extranodal natural killer (NK)/T-cell lymphoma, nasal type, ENKTCL-NT or NKTCL), a relatively rare subtype of non-Hodgkin lymphoma, is a class of neoplasms with special morphology, immunophenotype and biological behavior, which is highly aggressive, with rapid disease progression and poor prognosis (1-3). The disease often invades the upper respiratory tract such as the nasal cavity, paranasal sinuses, etc, causing severe damage to the soft tissues and bone. It is often manifested clinically by swelling of the soft tissues of the sinonasal tract, the outer nose and face, numbness, pain, and perforation of the nasal septum and (or) hard palate, with variable involvement of extranodal organs such as the skin, gastrointestinal tract, and testes also observed in some cases (4-8). The main treatments for limited-stage NKTCL are sequential therapy with chemotherapy followed by consolidative radiation; concurrent radiation and chemotherapy; or, in select situations and radiation therapy (RT) alone. The main treatment for advanced-stage NKTCL is chemotherapy (9). NKTCL tumor cells are positive for CD2 and CD56 expression and negative for CD3 expression on the cell surface, while the cytoplasm can express CD3 (10-12). Because NKTCL is difficult to obtain ideal clinical and pathological samples, it has caused certain obstacles to the research of the disease.

Studies have suggested that 8-17% of neoplastic cases are associated with inflammation caused by infection (13-15). The acute inflammatory response is conducive to efficient pathogen clearance and promotion of wound healing. However, when acute inflammation develops into chronic inflammation, it will create a microenvironment conducive to tumor initiation and progression. The association of chronic infections with tumors has been appreciated as early as the 20th century, and studies indicate that 15-20% of tumorigenesis is associated with chronic infections (16-18). For example, H. pylori infection is associated with gastric cancer (19). About 80% of hepatocellular carcinomas are associated with chronic infection with hepatitis B or C virus (HBV or HCV). About 70% of cervical cancers are associated with human papillomavirus type 16 or 18 infections (17, 20). Some lymphomas such as Burkitt's lymphoma, Hodgkin's lymphoma, and adult T cell lymphoma are all associated with some viral infections (21, 22). Chronic inflammation caused by chronic exposure to pathogenic microorganisms is a contributing factor of tumor occurrence. When an organism is invaded by a pathogen, it can rapidly synthesize and release chemical factors (e. g., CCL2 and CXCL8) and cytokines (e. g., IL-1, IL-6, and TNF-α). These factors are able to recruit and activate some immune cells with phagocytic effects to clear pathogens such as macrophages and neutrophils. However, when pathogens cannot be completely cleared, the continuous stimulation of pathogens can cause a large release of inflammatory factors, at which time the inflammatory response can cause harmful side effects to the body and may even cause tumorigenesis (23-25). In addition, after the resection of some primary tumors, tissue repair processes produce factors that promote vascularization such as vascular growth factor (VEGFR) and some cytokines such as transforming growth factor (TGF-β). These

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factors are able to promote the repair process of the tissues, but also contribute to the growth of tumor cells (26-29). In nasal NKTCL, a large number of acute or chronic reactive inflammatory cells can be seen under the microscope. These inflammatory cells can secrete a variety of cytokines, including IL-13, TNF-α, IL-4, IL-6, and IFN-γ (12, 14, 29). They are able to influence tumor tissue vascularity, lymphangiogenesis, and tumor cell apoptosis. Therefore, inflammatory factors play an important role in all processes of tumor initiation, progression, and metastatic spread.

Interleukin (IL)-22 is an effector cytokine and is normally produced by T lymphocytes and mucosal epithelial cells in assorted anatomic sites (30). Studies have indicated that IL-22 functions as the anti-inflammatory factor or proinflammatory factor in different diseases such as colitis, systemic lupus erythematosus, hepatitis and other inflammatory diseases (30, 31). The pro-inflammatory function of IL-22 is due to the induction of neutrophil recruitment chemokines in the skin, liver and gastrointestinal tract, and the production of acute phase response protein, which facilitates the activation of inflammatory T helper 17 (Th17) cells (32). IL-23 is a heterodimeric cytokine of the IL-12 superfamily that exhibits a proinflammatory role through its ability to contribute to the generation of Th17 cells (33). Clinically, IL-23 is overexpressed in a number of cancer types. Research shows that IL-23 can promote tumor metastasis by up-regulating angiogenesis factors (34). Overexpression of IL-23 can induce metastasis of hepatocellular carcinoma, colorectal cancer, melanoma, esophageal cancer and thyroid cancer (34). IL-17 is a proinflammatory cytokine first cloned in 1993 (35). The Th17 cells constitute a unique subset of CD4 T cells and are the major source of IL-17. Accumulating studies have suggested that IL-17 dysregulation is associated with the inflammatory diseases such as inflammatory bowel disease, psoriasis, rheumatoid arthritis, and asthma (36, 37). Up to date, the roles of IL-22, IL-23 and IL-17 have not yet been investigated, therefore, the current work aimed to explore the roles of IL-22, IL-23 and IL-17 in NKTCL, which might provide potential biomarkers for NKTCL.

Materials and Methods

Patients and clinical information

The experimental group consisted of 65 patients, all of whom were recruited from our hospital. The blank control group consisted of 60 healthy individuals from our hospital. Of these 65 patients with NKTCL, 45 were male and 20 were female, ranging in age from 12 to 76 years, with a median age of 44.3 years. Of these 60 healthy individuals, 40 were male and 20 were female, ranging in age from 12 to 75 years, with a median age of 43.8 years. Our study was approved by the Ethics Committee of the Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine, and all patients signed the informed consent. Experimental inclusion criteria: (1) The diagnosis of NKTCL was confirmed by pathological examination results according to the World Health Organization (WHO) classification method; (2) All patients had not received any previous antitumor therapy; (3) The follow-up examination was perfect; (4) Consent for collection of serum samples was obtained before receiving treatment. Exclusion criteria: (1) No risk factors in stage I; (2) Serious cardiopulmonary, renal, and liver dysfunction; (3) Pregnancy. In the early morning, 5 ml of venous blood of each candidate was collected by fasting, of which 2 ml was added to ethylenediaminetetra-acetic acid (EDTA) salt anticoagulation, and another 3 ml was allowed to stand, centrifuged, and the serum was extracted. After processing, the samples were kept in a -80 ℃ freezer for further use until enough samples were collected for detection.

ELISA

The levels of IL-22, IL-23, as well as IL-17 were determined by using enzyme-linked immunosorbent assay (ELISA) method with the IL-22 ELISA kit (PI595, Beyotime, Shanghai, China), IL-23 ELISA kit (PI660, Beyotime) and IL-17 ELISA kit (PI550, Beyotime). The procedures strictly followed the protocol provided by the manufacturer (Beyotime).

Statistical analysis

The obtained data were statistically analyzed with SPSS 22.0. All measurement data were expressed as mean ± standard deviation (x ± s), and Student's *t*-test was used for the analysis of differences between groups; $P < 0.05$ was taken to indicate a statistically significant difference.

Results

Clinical information of the patients

There were 65 patients in the experimental group, including 45 males and 20 females, with a male-to-female ratio of 2.25:1 and a median age of 44.3 years. Of these, 38 had B symptoms, 14 had regional lymphadenopathy, and 33 were Epstein-Barr virus (EBV) positive. Fifty patients had a good general condition, with an electrocorticography (ECoG) score of 0-1, while the remaining had a score of 2-3. Thirty-five had stage 1-2 disease and the remaining had stage 3-4 disease. Fifty-one had an the International Prognostic Index (IPI) score of 0-2 and the remaining had an IPI score of 3-4.

Serum IL-17, IL-22 and IL-23 were elevated in NKTCL patients

Furthermore, expression levels of IL-17, IL-22 and IL-23 in serum samples of the NKTCL patients as well as controls were compared. As indicated in Figures 1-3, a

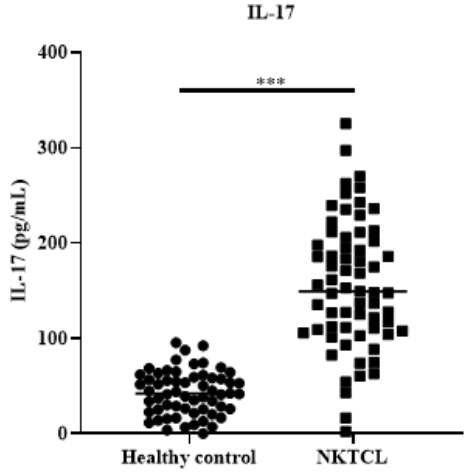

Figure 1. Comparison of the levels of IL-17 between control and NKTCL patients. ***P<0.001.

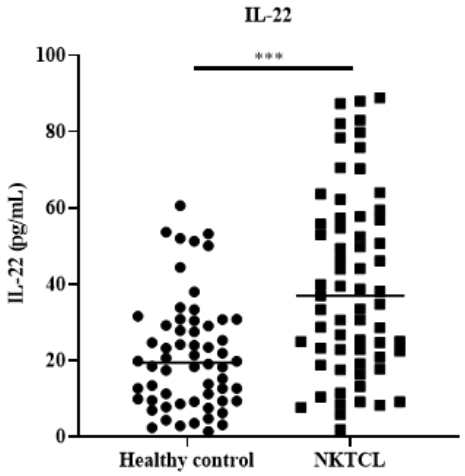

Figure 2. Comparison of the levels of IL-22 between control and NKTCL patients. ***P<0.001.

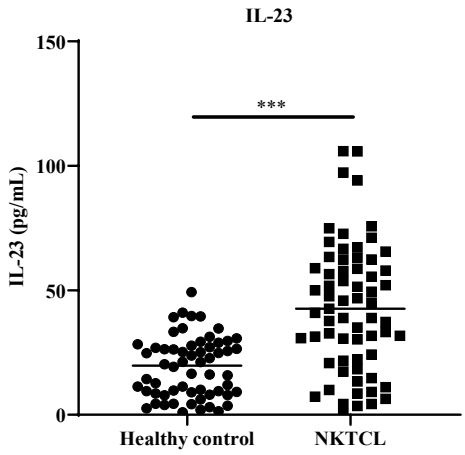

Figure 3. Comparison of the levels of IL-23 between control and NKTCL patients. ***P<0.001.

total of 65 patients with NKTCL had IL-17 levels in serum (156.0 ± 67.75) pg/mL, IL-22 levels (39.98 ± 23.88) pg/mL, and for IL-23 the level was (43.05 ± 25.69) pg/mL. A total of 60 normal controls had serum levels of IL-17 (42.68 ± 23.05) pg/mL, IL-22 (21.45 ± 14.68) pg/mL, and the IL-23 level was (19.01 ± 12.10) pg/mL. IL-17 in normal human serum was significantly lower than that in NKTCL patients (P<0.001). IL-22 (P<0.001) and IL-23 (P<0.001) in the serum of NKTCL patients were also significantly higher than the normal subjects.

Potential diagnostic value of IL-17, IL-22 and IL-23 for NKTCL

Finally, we performed the receiver-operating characteristic curve (ROC) analysis to evaluate the potential diagnostic value of IL-17, IL-22 and IL-23 for NKTCL. As displayed in Figure 4-6, we found that the AUC of IL-17 was 0.9487 (95% confidence interval (CI), 0.9052 to 0.9922), the IL-22 was 0.7321 (95% CI, 0.6449 to 0.8192), and the IL-23 was 0.7885 (95% CI, 0.7070 to 0.8699). These data suggested IL-17, IL-22 and IL-23 were all sensitive biomarkers for NKTCL.

Discussion

NKTCL is relatively rare, and its pathogenesis is not fully understood. The current study found that EBV infection is closely related to NKTCL pathogenesis, especially occurring in nasal cases, and EBV infection is present in 80% - 100% of cases, while the detection rate of EBV in NKTCL patients occurring in extranasal locations is relatively low (38, 39). Currently, NKTCL still lacks standard treatment regimens. Inflammation is a complex defensive

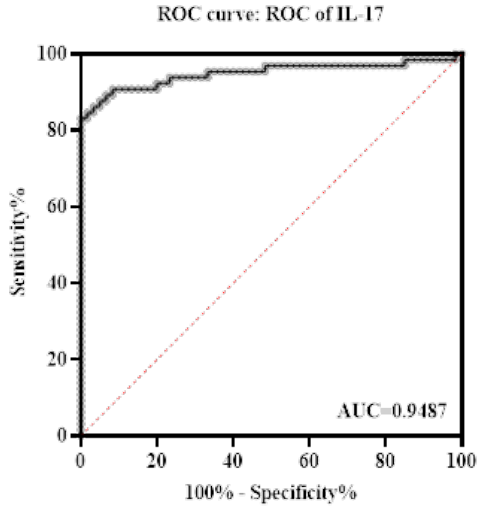

Figure 4. ROC of IL-17.

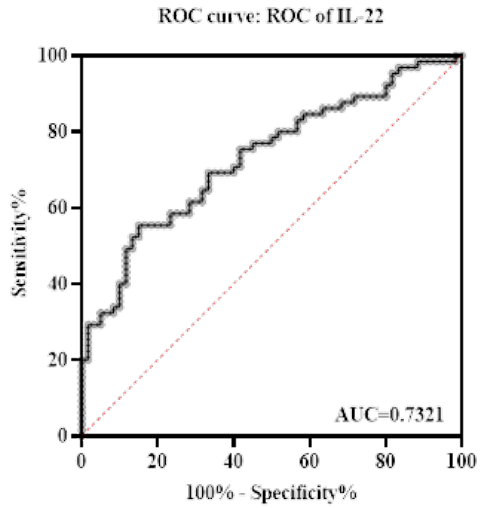

Figure 5. ROC of IL-22.

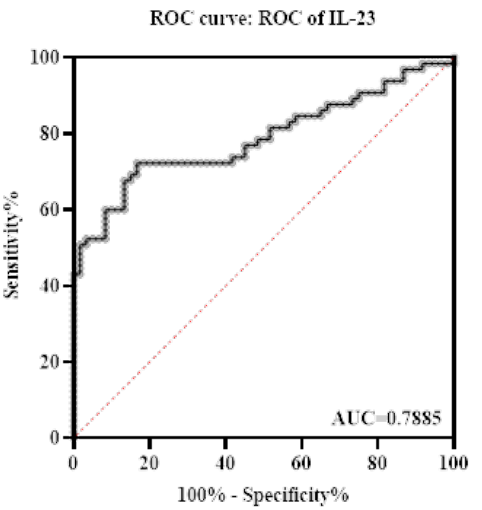

Figure6. ROC of IL-23.

response that occurs in living tissues with a vasculature to damaging agents. The observation of infiltrating leukocytes in tumor tissues by Rudolf Virchow in 1863, whereby it was speculated that tumors may originate from a chronic inflammatory response (19, 21, 40), has since significantly linked tumor origin to chronic inflammation. Most people believe that a single cell proliferation does not lead to tumorigenesis, but a large number of infiltrated inflammatory cells and their secreted cytokines do have an important role in tumorigenesis and progression. Notably, NKTCL is an aggressive lymphoma closely related to EBV and characterized by varying degrees of systemic inflammation (41). Studies have shown that the pathogenesis of NKTCL may be related to the involvement of factors involved in various immunological aspects such as Th17 and associated cytokines. Th17 cells are a new subset of Th cells related to inflammatory and autoimmune diseases recognized in 2005. Its main feature is the secretion of IL-17A. In addition, differentiated and mature Th17 also secretes several cytokines such as IL-6, IL-21, IL-22, IL-23, and so on, which mediate the production of inflammatory diseases (18, 42, 43).

Recently, it is reported that the concentration of Th17 cells and related cytokines (IL-17, IL-22 and IL-23) are significantly increased in some tumors. However, in liver cancer, the poor prognosis of patients is more related to Th17 / IL-17 in the tumor microenvironment (44, 45), and the crucial function of Th17 / IL-17 on aggravating liver disease and promoting inflammation has also been reported (46-48). Several studies have suggested that IL-22 plays a protective role in hepatocyte injury and is able to promote hepatocyte regeneration (49-51). Furthermore, the IL-22 receptor is highly expressed in hepatocytes, suggesting that the important effector cells of IL-22 are hepatocytes. Moreover, IL-22 is important in establishing the tumor microenvironment for cutaneous T-cell lymphoma (51). In addition, Jun Ho Yi et al have pointed out that patients with peripheral T-cell lymphoma have elevated expression of IL-17 and IL-23 (52). Studies have found that NKTCL is a typical malignancy occurring on a background of chronic inflammation. Cancer-related inflammation is associated with STAT3 signaling and important cytokines such as IL-23, and it may be a new direction for cancer treatment (53, 54). Many studies have found that Th17 cells undergo differentiation and migration changes under the influence of cytokines, which affect the sprouting growth of tumors (55). In the current work, we found that serum IL-17, IL-22 and IL-23 were elevated in NKTCL patients. More importantly, the ROC results suggested that IL-17, IL-22 and IL-23 could distinguish NKTCL patients from healthy controls. These results suggested that IL-17, IL-22 and IL-23 could serve as potential diagnostic biomarkers for NKTCL. But the specific mechanism should be investigated in future works.

There are several limitations in our paper. First, the samples of our study were small. In addition, the biological role of IL-17, IL-22 and IL-23 in NKTCL was not investigated. Therefore, more relevant experiments should be carried out to perfect our study.

In conclusion, we proved for the first time that IL-17, IL-22 and IL-23 were significantly up-regulated in patients with NKTCL, and our results have provided novel evidence that IL-17, IL-22 and IL-23 were sensitive biomarkers for the early diagnosis of patients with NKTCL.

Conflict of interest

None.

Acknowledgement

None.

Data Availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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