Chronic active EBV infection with hemophagocytic lymphohistiocytosis and progression to aggressive NK cell leukemia

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Abstract

Background:The clinical trend of EBV infected patients has been always the focus of attention. Case presentation: We report a rare case of chronic active EBV infection (CAEBV) with hemophagocytic lymphohistiocytosis progressed to childhood aggressive NK cell leukemia and cured by allogeneic hematopoietic stem cell transplantation. Conclusions: The EBV infection of T/NK cells can lead to CAEBV, and if the T/NK cells carry HLH related gene mutation, it is easy to accompany with the hemophagocytic syndrome, and this type of CAEBV may rapidly progress to ANKL or other neoplastic diseases. Therefore, we should reinforce the knowledge on this kind of patients to receive appropriate and timely treatment.

Chronic active EBV infection with hemophagocytic lymphohistiocytosis and progression to aggressive NK cell leukemia: a case report

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Abbreviations

Abbreviations	Full term
CAEBV-T/NK	Chronic active EBV infection of T-cell or NK-cell type
ANKL	Aggressive natural killer cell leukemia
ENKTL	Extranodal NK/T cell lymphoma
FHL	Familial hemophagocytic lymphohistiocytosis
HLH	hemophagocytic lymphohistiocytosis

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Abstract

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Case presentation: We report a rare case of chronic active EBV infection (CAEBV) with hemophagocytic lymphohistiocytosis progressed to childhood aggressive NK cell leukemia and cured by allogeneic hematopoietic stem cell transplantation.

Conclusions: The EBV infection of T/NK cells can lead to CAEBV, and if the T/NK cells carry HLH related gene mutation, it is easy to accompany with the hemophagocytic syndrome, and this type of CAEBV may rapidly progress to ANKL or other neoplastic diseases. Therefore, we should reinforce the knowledge on this kind of patients to receive appropriate and timely treatment.

Background

The clinical trend of EBV infected patients has been always the focus of attention. It is extremely difficult to identify which patients may resolve spontaneously or proceed to chronic stage or proceed rapidly. Here we report a rare case of chronic active EBV infection (CAEBV) with hemophagocytic lymphohistiocytosis progressed to childhood aggressive NK cell leukemia and cured by allogeneic hematopoietic stem cell transplantation. we should reinforce the knowledge on this kind of patients to receive appropriate and timely treatment.

Case presentation

A 7-year-old boy developed recurrent fever and hypersensitivity to mosquito bites one year ago. The symptoms persisted for three months and then resolved without any treatment.

During the two months before admission, the patient showed no obvious emergence of recurrent fever, with his highest temperature being 39. Physical examination showed that the left cervical lymph node was enlarged having a diameter of 1.2 cm and hepatosplenomegaly was also detected. After admission, the biopsy of the enlarged lymph node was performed. Four months later, the patient presented with fever and hepatosplenomegaly again, and a peripheral blood lymphocyte smear was conducted this time. The child did not possess any immunodeficiency.

The results of laboratory tests conducted after patient admission are listed in Table 1. Blood tests showed a reduction in all three blood cell lines. The NK cell activity was lower than the normal value, whereas the other indexes related to hemophagocytic syndrome, such as the levels of soluble CD25 and CD163 were significantly higher than the normal. The content of serum ferritin was shown to be significantly increased. The EB virus encoded DNA was also detected in the peripheral blood.

The biopsy of the lymph node showed that the paracortical area of the lymph node was hyperplastic and the marginal and medullary sinuses were open (Figure 1a). Lymphocytes vary in size and are interspersed with a small number of immunoblasts and plasma cell (Figure 1b). Furthermore, the hyperplasia of histiocytes

could be detected in the opened lymphatic sinuses, and the phenomenon of histiocyte swallowing red blood cells was distinctly observed (Figure 1c).

Immunohistochemistry showed that CD20 positive cells were predominantly located in the follicular area (Figure 2a). CD3 and CD5 was positive in the interfollicular and paracortical areas (Figure 2b, 2c). The ratio of CD4: CD8 T cells was around 2:1 (Figure 2d, 2e). CD56 was positive in a small number of scattered cells (Figure 2f). CD30 was positive in transformed large cells (Figure 2g). The proliferation index of Ki67 in the interfollicular zone was found to be around 10% (Figure 2h). In situ hybridization showed that the cells in the interfollicular zone were Epstein-Barr virus encoded RNA (EBER) positive (Figure 2i). The gene rearrangement detection showed that TCRγ and IgH were negative.

Combined with clinical data, the pathological diagnosis of the lymph node was analysed as systemic chronic active EBV infection-T/NK cell phenotype (CAEBV-T/NK) with hemophagocytic lymphohistiocytosis (HLH). After diagnosis, the patient accepted chemotherapy and reached complete remission (CR).

Four months after being discharged from the hospital, the patient developed fever and hepatosplenomegaly again, and underwent a peripheral blood separated lymphocyte smear.

The smears were found to be densely packed with lymphoid cells, and the features of these lymphoid cells were medium in size, uniform in shape, and irregular in nucleus (Figure 3a). Degeneration was observed in some cells. Immunohistochemistry showed striking positivity in lymphoid cells for CD3ε (Figure 3b), granzyme B (Figure 3c) and CD56 (Figure 3d), and in situ hybridization showed EBER was positive (Figure 3e).

Combined with the clinical characteristics, the aggressive clinical course, the systemic symptoms and the neoplastic NK cells in the peripheral blood, the pathological diagnosis was aggressive natural killer cell leukemia (ANKL).

In time, the gene mutation detection was performed, and a UNC13D gene heterozygous mutation was detected in the patient as well as his father.

Follow-up: The patient underwent allogeneic hematopoietic stem cell transplantation and had CR currently.

Discussion

This is a rare case of childhood aggressive NK cell leukemia (ANKL). It demonstrates the process of CAEBV-T/NK with hemophagocytic syndrome progressed to ANKL, additionally,it is a rare case that cured by allogeneic hematopoietic stem cell transplantation.

Chronic active EBV infection of T-cell or NK-cell type (CAEBV-T/NK) is a systemic EBV-positive polyclonal, oligoclonal, or monoclonal lymphoproliferative disorder[1]. It shows a broad spectrum of clinical manifestations, from localized to more systemic diseases. The Local symptoms are mainly cutaneous lesions, such as hydroa cacciniforme-like lymphoproliferative disorder and severe mosquito bite allergy[2]. The systemic CAEBV-T/NK is characterized by fever, hepatosplenomegaly, and lymphadenopathy, with or without any cutaneous manifestations[1,3]. The prognosis of CAEBV-T/NK in children is significantly different from that in adults, and the prognosis in adults is relatively worse[3,4]. In the literature, 16% of CAEBV-T/NK can progress to extranodal NK/T cell lymphoma (ENKTL) or ANKL, which is more common in adults and rare in children[1,3-5]. However, due to their rarity, Criteria to separate clinical risk groups at diagnosis are confounded by lack of markers to reliably predict clinical behavior that ranges from self-limiting proliferations to those that are rapidly fatal[6-8].

Although it has been reported that HLH occurs in 24% of CAEBV-T/NK cases, and the presence of hemophagocytosis is an indicator of worse overall clinical outcome of CAEBV-T/NK, not all CAEBV-T/NK with HLH will progress to invasive lesions[1,9,10]. The occurrence of our case suggests that patients with hemophagocytic genetic abnormalities in CAEBV-T/NK are more likely to progress to invasive disease if they develop HLH. The case carries a heterozygous mutation in the *UNC13D* gene and therefore does not meet the diagnosis of familial hemophagocytic lymphohistiocytosis (FHL), which should be secondary

forms of HLH[9-12]. But it unknown if susceptibility to developing HLH is caused by genetic predisposition or EBV-induced immunological dysregulation, or a combination of the two[12-14].

UNC13D and other HLH related genes encode proteins involved in intracellular vesicle trafficking, and their mutations lead to defective cytotoxicity,The protein products of these genes are critical for normal cytotoxic granule exocytosis. In patients with defects in these genes, granule contents do not get released into the immunological synapse, and target cells are not able to be killed[11]. Furthermore, in our as yet unpublished study of ANKL gene mutation sequencing, the mutation rate of cytotoxic granulocyte exocytosis related genes reached 12%. So we speculate that these genes may play an important role in the tumorigenic transformation of NK cells.

ANKL is a rare form of neoplasm. We have reported 35 ANKL cases diagnosed by the Department of Pathology of West China Hospital. The median age of onset was 35 years and the median survival time was only 43 days[15]. The WHO classification mentioned that the median age of ANKL is 40 years[16]. Therefore, ANKL mainly occurs in young and middle-aged people, and it's rare in children. Also, because of the highly invasive nature of ANKL, the prognosis is very poor. Most victims die before or during chemotherapy, and few survive to the stage of stem cell transplantation[15]. This patient had complete remission after timely hematopoietic stem cell transplantation. It suggests that hematopoietic stem cell transplantation is an effective treatment option for patients with aggressive NK cell leukemia, especially those who have developed CAEBV with hemophagocytic syndrome.

Conclusion

The EBV infection of T/NK cells can lead to CAEBV, and if the T/NK cells carry HLH related gene mutation, it is easy to accompany with the hemophagocytic syndrome, and this type of CAEBV may rapidly progress to ANKL or other neoplastic diseases. Thus, it is essential to recognize these CAEBV-T/NK cases to guide the selection of therapeutic strategy and to avoid treatment delay.

Ethics statement

Written informed consent was obtained from the kin of the patient for publication of this case report and accompanying images.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Authors' contributions

LM Gao and HF Li made contributions to acquisition of clinical data, and manuscript writing. WP Liu, S Zhao,WY Zhang, Q Li and ZH Chen participated in design of the study and helped to confirm the diagnosis. VA De souza and BA Biju helped to manuscript writing. All authors read and approved the final manuscript.

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Figures legend

Figure 1. The histopathology of the lymph node. The paracortical area of the lymph node was hyperplastic and the marginal and medullary sinuses were open (Figure 1a). Lymphocytes vary in size and are interspersed with a small number of immunoblasts and plasma cell (Figure 1b). The hyperplasia of histiocytes could be detected in the opened lymphatic sinuses, and the phenomenon of histiocyte swallowing red blood cells was distinctly observed (Figure 1c).

Figure 2. Immunohistochemistry result of the lymph node. CD20 positive cells were predominantly located in the follicular area (Figure 2a). CD3 and CD5 was positive in the interfollicular and paracortical areas (Figure 2b, 2c). The ratio of CD4: CD8 T cells was around 2:1 (Figure 2d, 2e). CD56 was positive in a small number of scattered cells (Figure 2f). CD30 was positive in transformed large cells (Figure 2g). The proliferation index of Ki67 in the interfollicular zone was found to be around 10% (Figure 2h). In situ hybridization showed that the cells in the interfollicular zone were EBERpositive (Figure 2i).

Figure 3. The morphology and Immunohistochemistry result of peripheral blood separated lymphocyte smear . The features of densely packed lymphoid cells were medium in size, uniform in shape, and irregular in nucleus (Figure 3a). Immunohistochemistry showed striking positivity in lymphoid cells for CD3ε (Figure 3b), granzyme B (Figure 3c) and CD56 (Figure 3d), and in situ hybridization showed EBER was positive (Figure 3e).

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`table1. The results of laboratory tests of peripheral blood..doc` available at https://authorea.com/users/732745/articles/710903-chronic-active-ebv-infection-with-hemophagocytic-lymphohistiocytosis-and-progression-to-aggressive-nk-cell-leukemia