Aggressive Natural Killer Cell Leukemia Secondary to Hodgkin Lymphoma: a Case Report and Review of the Literature

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Introduction

Aggressive Natural Killer Cell Leukemia (ANKL) is a rare disease, characterized by a clonal proliferation of neoplastic Natural Killer (NK) cells and a highly malignant clinical progression [1-8]. The diagnosis of ANKL is made usually by combining clinical presentations with the morphologic and immune-phenotypic features of neoplastic NK cells [1,7,9]. ANKL patients often present with high fever, poor performance status, pancytopenia, hepatosplenomegaly, coagulopathy, multiple organ failure, and haemophagocytic syndrome [2, 8]. The disease shows a highly aggressive clinical phenotype: most patients die within 2 months from diagnosis [2,10,11]. Up to now, there is no standardized therapeutic regimen to effectively control the progression of this disease, thus leading to a very poor clinical prognosis.

ANKL is more prevalent in Asian population than other ethnic groups. Previously, we have reported 29 de novo ANKL cases and summarized their clinical features along with laboratory findings [8]. NK cells show unique immunophenotypic features: CD2+ CD3- CD4- CD5- CD56+ CD57-, typically with high Ki-67 (>40%) [8]. However, ANKL secondary to other diseases has never been documented. To our knowledge, the case we reported here is the first case that developed secondary ANKL after the treatment of Hodgkin Lymphoma.

Case report

In December 2012, a 32-year old Chinese female was admitted to Oncology Department of Tongji Hospital (Wuhan, China) due to cervical mass and splenomegaly. Right cervical mass biopsy revealed classic Hodgkin Lymphoma with mixed cellularity, “Classic Hodgkin Lymphoma stage IIIA” diagnosis was made by combining clinical presentations and laboratory data [Figure 1(a)]. She received 3 cycles of DICE chemotherapy (Dexamethasone 10mg i.v. daily for 4 days, Ifosfamide 1500 mg continuously infused daily for 4 days, Cisplatin 38 mg i.v. each day for 4 days, Etoposide 90 mg continuously infused i.v. daily for 4 days). However, after the third cycle of DICE, the patient started having a recurring fever, insensitive to antibiotics. Upon admission, multiple enlarged lymph nodes involving cervical, axillaries, supraclavicular fossa presented. Fine-needle biopsy of right axillary lymph node showed a large number of blast cells and some phagocytes. The patient was then diagnosed the relapse of Hodgkin Lymphoma and further treated with 3 cycles of DICE chemotherapy (Dexamethasone 10mg i.v. daily for 4 days, Ifosfamide 1500 mg continuously infused daily for 4 days, Cisplatin 38 mg i.v. each day for 4 days, Etoposide 90 mg continuously infused i.v. daily for 4 days). In December 2014, the patient started having a recurring fever, insensitive to antibiotics. She was admitted to Oncology Department of Tongji Hospital (Wuhan, China) due to cervical mass and splenomegaly. Right cervical mass biopsy revealed large malignant cells known as Reed-Sternberg cells (RSC) (arrow). The diagnosis of ANKL is made usually by combining clinical presentations with the morphologic and immune-phenotypic features of neoplastic NK cells [1,7,9]. ANKL patients often present with high fever, poor performance status, pancytopenia, hepatosplenomegaly, coagulopathy, multiple organ failure, and haemophagocytic syndrome [2, 8]. The disease shows a highly aggressive clinical phenotype: most patients die within 2 months from diagnosis [2,10,11]. Up to now, there is no standardized therapeutic regimen to effectively control the progression of this disease, thus leading to a very poor clinical prognosis.

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In conclusion, improvements of combined therapy as well as close monitoring during clinical follow up could warrant the improved overall survival of HL and prevent fatal complications.
patient once again presented with fever. After administration of antibiotics, her fever failed to subside and multiple lymphadenopathy was not resolved. Soon after, she was referred to the Hematology Department due to progressive fatigue and shortness of breath.

On admission, she presented with high fever (39°C), lymphadenopathy, hepatosplenomegaly. Blood test showed elevated white blood cells (14.98×10^9/L) with 2% of blast cells; low hemoglobin (67 g/L) and platelet (30×10^9/L); increased ferritin (2322.5 g/L), lactate hydrogenase (2460 U/L), triglyceride (3.57 mmol/L), and low level of fibrinogen (0.95g/L). She was found to have a high copy number of serum EB virus DNA (>1.0×10^7 IU/mL). Peripheral blood smear showed 17% of blast cells [Figure 1(b)]. Peripheral blood phenotyping revealed 3.4% of T cell lymphocytes (CD3+CD2+CD5+CD7+) and 28.19% of abnormal NK cells (CD2+CD3-CD56+CD5-CD45RA+CD94+, Ki67 32.8%) [Figure 1(c)]. Chest CT showed right pleural effusion and pulmonary infection. Thoracentesis was performed and pleural fluid was subjected to cell morphology and flow cytometry analysis. Under microscopy, there were 17% lymphocytes and 65% abnormal cells. Immunophenotype of cells from pleural fluid showed 67% of abnormal NK cells (CD2+CD3-CD56+CD45RO+HLADR+CD94+, Ki67 56%).

Thus the patient was diagnosed with Hodgkin Lymphoma, secondary NK cell leukemia and Haemophagocytic Lymphohistiocytosis (HLH). She was treated with Dexamethasone, Etoposide and IVIG following HLH 2004 protocol, as well as blood transfusion and a few courses of antibiotics, but her condition kept deteriorating. Unfortunately, 6 days after admission, the patient's next of kin signed a “Do Not Resuscitate” (DNR) form and gave up all treatments.

**Discussion**

ABVD chemotherapy regimen followed by involved-field irradiation is the standard treatment for HL patients, effective in both early and advanced stages [12]. However, the toxicity of chemotherapy and radiotherapy should never be ignored. According to NCCN guidelines, developing secondary tumor is one of the most severe complications of HL during clinical follow up [12]. In HL patients, the risk of developing secondary lung and breast cancer are highly relevant to irradiation therapy (RT). In contrast, therapy-related acute leukemia and myelodysplastic syndromes (t-AML/MDS) usually result from the application of alkylating agents (AA) in chemotherapy [13-16]. Acute leukemia has the highest relative mortality of all second malignancies [14]. A German Hodgkin Study Group concluded that t-AML/MDS represents rare but severe late sequence of HL, the prognosis is overall very poor despite that selected patients may be rescued by allogeneic hematopoietic stem cell transplantation (allo-HSCT) [13,17].

The risk of developing t-AML/MDS is related not only to the primary therapy, but also to therapy at relapse. Several studies indicate that the number of chemotherapy cycles to achieve remission correlates with the risk of secondary leukemia [18-20]. Since the 1980s, MOPP regimen has gradually been replaced by ABVD, which contains less AA, and several multi-centered surveys suggest that ABVD led to a lower risk of developing acute leukemia as compared to MOPP.
[14,21,22]. Nonetheless, there are limited data concerning the incidence of hematologic malignancies following ABVD [15,23]. Here we report a case of a patient that developed ANKL, a highly aggressive hematological malignancy, after the initial remission of HL. To our knowledge, this is the first report of secondary ANKL after chemotherapy and radiation treatments.

The pathobiology of HL remains poorly understood. The role of Epstein-Barr virus (EBV) infection in the development of HL is still under investigation. EBV, a ubiquitous herpes virus, is the first identified human virus with a proven association with carcinogenesis [24,25]. Although T-cell and NK cell can also be infected by EBV, it mainly attacks B lymphocytes, thus the most common forms of EBV-associated lympho-proliferative disorders are B-cell lymphomas such as HL, Burkitt Lymphoma and diffuse large B-cell lymphoma (DLBCL) [24-27]. In nearly half of HL patients, the genome of EBV can be found [28-30]. Notably, EBV is more commonly associated with mixed-cellularity HL and lymphocyte-depleted HL [28-30]. Therapeutic regimen for both EBV positive and negative cases of HL is currently identical, with long term remissions in most patients, but relapsed EBV positive HL patients have a poor prognosis [29,31]. Here, the patient was originally mixed-cellularity HL, her EBV copy number was >1.0×107 IU/mL when the secondary ANKL occurred although the primary level of EBV at diagnosing HL was unclear.

Most interestingly, ANKL is also associated frequently with EBV infection. In fact, high EBV copy number is one of most important clinical features, which helps establish the diagnosis of ANKL. EBV is nearly always detected in the neoplastic tissues and peripheral blood (PB) of ANKL and the titers of EBV varied as the disease progressed and improved [8]. Thus it is of great interest whether the EBV level should be followed from the time point of diagnosing EBV positive HL throughout routine clinical follow-up. In addition, whether ABVD regimen is effective in eradicating EBV infection is yet to be investigated.

To date, the duration of effect how certain alkylating agents lead to therapy-related malignancies remains poorly understood. In order to early detect secondary malignancies, clinical evaluations are recommended at 3-4 month intervals during the first and second year following completion of therapy, also at 6-month intervals in the third to fifth year and annually thereafter [12]. However, guidelines with regards of screening scope vary widely. According to NCCN guidelines, annual chest imaging (chest radiograph or CT) and breast screening (mammography or MRI) are suggested [12]. As secondary hematological malignancies were not uncommon following HL treatment, regular bone marrow examination may be also recommended to early define such abnormalities. Given the important role of EBV in the pathogenesis of HL, monitoring the titer of EBV may be worthwhile throughout the treatment of EBV positive HL. Although HL patients with high EBV copy number often have poorer prognosis, whether it could lead to higher chances of second malignancies is yet to be studied.

Treatment-related cancers are a major problem in HL survivors. Novel treatment strategies for HL should aim at a reduction of chemotherapy and RT in order to reduce the risk for developing therapy-related malignancies. For example, the clinical trials data from Stanford University revealed that limiting the dose of AA have significantly reduced the incidence of t-AML/MDS [19]. With the development of modern approaches in management of HL, anticipated cure rates of HL must be balanced with the unintended sequelae of therapy. Meanwhile, bone marrow and EBV examinations during clinical follow up might be worthwhile to monitor in order to early define secondary hematological malignancies and therefore prevent fatal complications.

Acknowledgments

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References


