Case Report

Rapid and fatal progression of Epstein-Bar virus-associated paracortical hyperplasia with T-cell oligoclones to overt angioimmunoblastic T-cell lymphoma: a case report

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Abstract: We report an unusual case of angioimmunoblastic T-cell lymphoma (AITL) progressing rapidly from Epstein-Bar virus (EBV)-associated paracortical hyperplasia with T-cell oligoclones, which caused the patient to die within only 1 month. The patient was a 67-year-old Chinese man with 3 month's history of rhinorrhea, pruritus and superficial lymphadenopathy. In the first biopsy, morphology and immunophenotype showed reactive lymphoid hyperplasia predominated by paracortical hyperplasia. In situ hybridization of EBER and TCR gene rearrangement analysis demonstrated infection of EBV and rearrangements of TCRβ-VJ2, TCRβ-DJ and TCRγ-VJ2 genes. After about one month's effective treatment of antiviral therapy, the patient's condition deteriorated with extensive systemic symptoms. In the second biopsies of two involved sites, the findings of morphology, immunophenotype and genetics resulted in the diagnosis of AITL. Although received chemotherapy of COP immediately, the patient died of complications of AITL less than one month later.

Keywords: Angioimmunoblastic T-cell lymphoma, lymphoid hyperplasia, paracortical hyperplasia, Epstein-Bar virus

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) was first described as a distinct clinicopathologic entity in 1974, which accounts for approximately 1%-2% of non-Hodgkin's lymphomas. AITL ranks second in peripheral T-cell lymphomas (PTCLs) worldwide. Geographically, it appears more prevalent in Europe (29%) than North America (16%) or Asia (18%). In the past, AITL was felt to be an atypical reactive process, with an increased risk of progressing to lymphoma. Terms frequently used to describe AITL included angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), immunoblastic lymphadenopathy, lymphogranulomatosis X and AILD-type T-cell lymphoma. Overwhelming evidence proved AITL to be a de novo peripheral T-cell lymphoma, which was considered as a distinct entity in the 2008 WHO classification [1-4].

Most patients of AITL have a rapid clinical course, and 90% are at stage III or IV at pre-

sentation. The median survival is less than 3 years. The majority of deaths are due to infectious complications rather than progressive lymphoma, which makes AITL particularly difficult to treat with chemotherapy. Rare patients may have expanded EBV-positive clones that lead to EBV-positive large B-cell lymphomas [3-6].

Here, we show a unique case of AITL, which only lasted 6 months from onset to death. The patient presented with morphological and phenotypical feature of lymphoid hyperplasia with rearrangements of three TCR genes and progressed rapidly to overt AITL. The patient died of complications caused by AITL less than one month after the diagnosis of AITL.

Case report

A 67-year-old Chinese male with a 3-month history of rhinorrhea, pruritus and superficial lymphadenopathy (cervical lymph nodes painful, axillary and inguinal painless) sought care
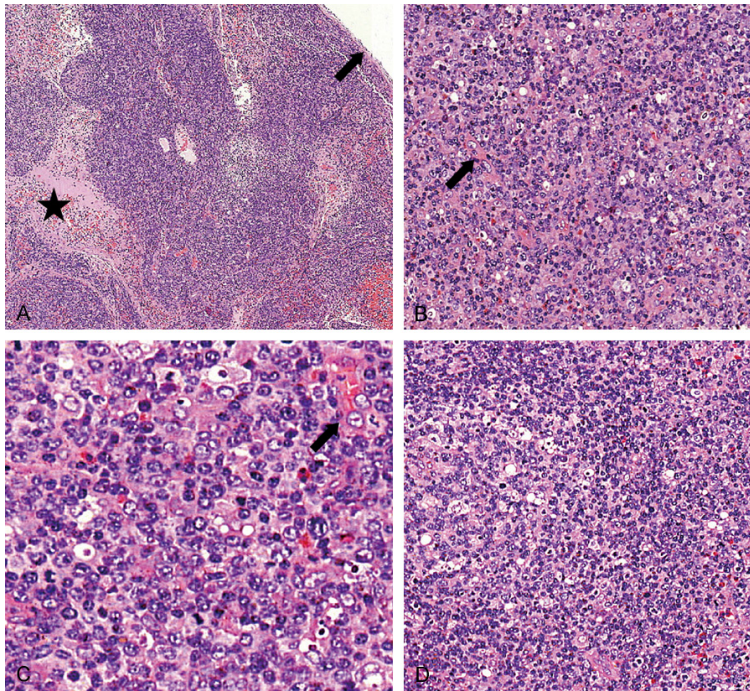
Figure 1. Morphological features of the cervical lymph node in the first admission. (A) The lymph node architecture was preserved, with slim capsule (arrow) and dilated sinuses (asteroid) (HE, original magnification, ×20). (B and C) In the paracortical area, there was a polymorphic infiltration of small, medium, and large-sized lymphocytes intermingled with histiocytes, eosinophils, plasma cells. No atypical lymphoid cells were observed, and arborizing postcapillary high endothelial venules (HEVs) were prominent (arrow in B and C) (B. HE, original magnification, ×200; C. HE, original magnification, ×400). (D) An expanded follicle is shown (HE, original magnification, ×200).

positive EB core antibody and elevated C-reactive protein. The ulcers in duodenal bulb and a left axillary lymph node were biopsied and diagnosed as angioimmunoblastic T-cell lymphoma (AITL). Although the patient received COP (cyclophosphamide, vincristine, prednisone) chemotherapy subsequently, his condition deteriorated progressively with larger lymph nodes, edema, hyperpyrexia, dyspnea and shock. On 9 August 2013, the patient died of respiratory and circulatory failure caused by AITL.
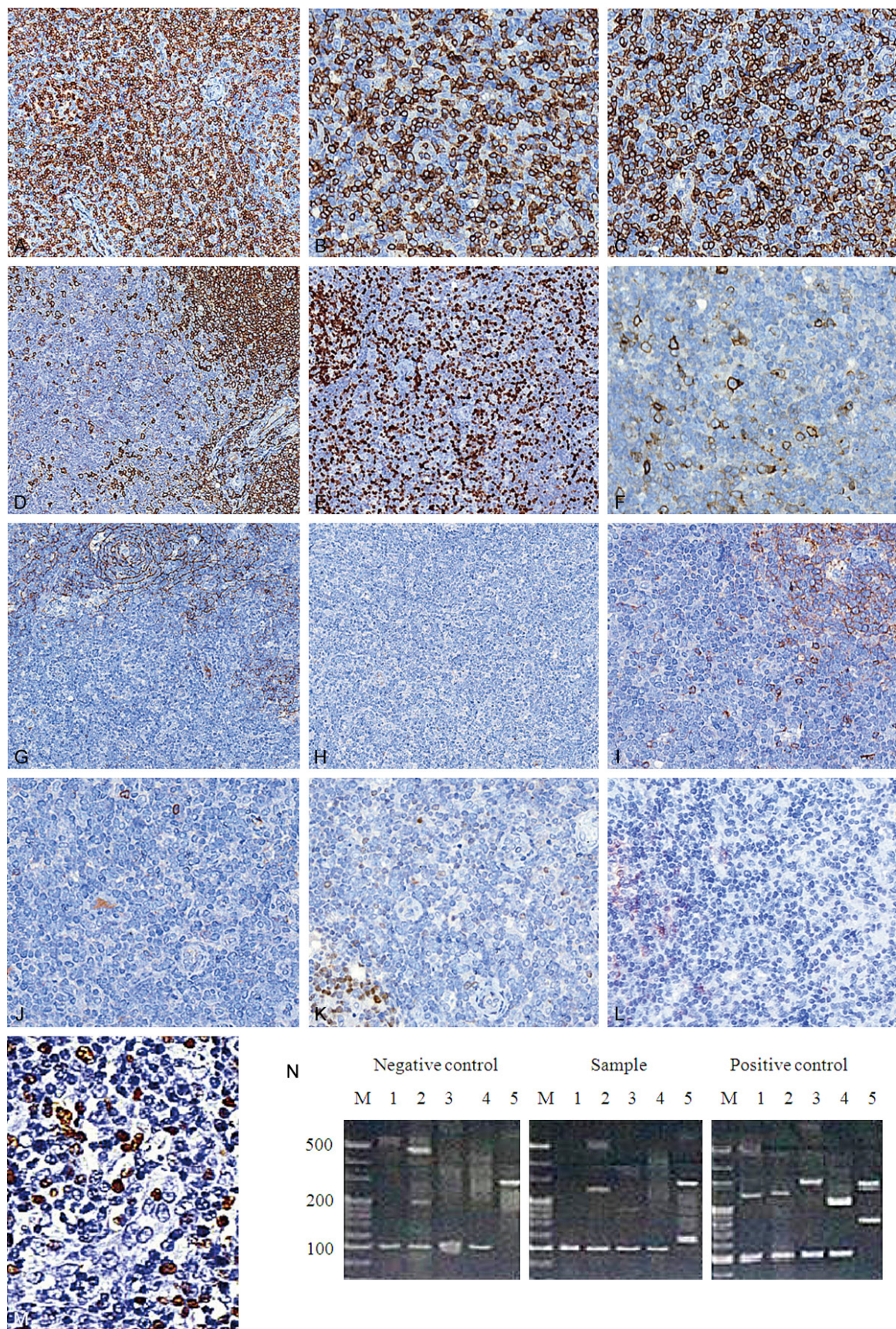
Morphology, immunophenotype and genetics of the cervical lymph node in the first admission

HE staining of the cervical lymph node biopsy revealed a lymphoid hyperplastic feature, predominated by paracortical hyperplasia (**Figure 1**). The lymph node architecture was preserved with slim capsule, dilated sinuses and expanded paracortical zone. The paracortical zone was characterized by a heterogeneous population of small, medium and large lymphocytes admixed by immunoblasts, histiocytes, eosinophils and plasma cells, accompanied by numerous arborizing postcapillary high endothelial venules (HEVs). Only a few follicles were present, some shrinked, and some expanded. No atypical lymphoid cells were observed.

Immunohistochemical staining showed the reactive interfollicular areas were predominently CD3-positive T lymphocytes expressing CD4 and CD8 polyclonally, scattered by a few CD20-positive B lymphocytes. The Ki-67 proliferative index in the paracortical zone varied from 30% to 70%. CD30 of various intensities labelled activated immunoblasts. The follicular dentritic meshwork stained by CD21 extended barely from the follicles, sparing the interfollicular zone intact. There were no positive markers (CD10, BCL6, CXCL13) of angioimmunoblastic T-cell lymphoma (**Figure 2A-L**). In situ hybridi-

on 2 May 2013. A swelling cervical node was biopsied and interpreted as lymphoid hyperplasia predominated by paracortical hyperplasia. After admission on 10 May 2013, the patient was given ganciclovir and dexamethasone. 8 days later, the enlarged lymph nodes reduced in size and the patient was discharged. After half a month, the superficial nodes waxed again, which waned when the patient was treated with oral famciclovir and dexamethasone. A week later, the superficial lymph nodes swelled again accompanied with chills, fever and bellyache, and the swelling lymph nodes didn't respond to antiviral therapy this time. Therefore, the patient re-hospitalized on 21 July 2013. Computerized tomography revealed bilateral hydrothorax, hydropericardium, ascites, and multiple nodules in spleen, liver, hilarregion, retroperitoneal part and retrosternal area. Gastroscope showed two ulcerations in duodenal bulb, both about 1 cm in diameter. Positive laboratory findings included serum lactate dehydrogenase of 1558 U/L,

Figure 2. Immunophenotype and genetics of the cervical lymph node in the first admission. (A-F) The extended interfollicular areas were predominently occupied by CD3-positive T lymphocytes (A. ×100), which polyclonally expressed both CD4 (B. ×200) and CD8 (C. ×200) and were scattered by a few CD20-positive B lymphocytes (D. ×100). In the interfollicular zones, Ki-67 proliferative index ranged from 30% to 70% (E. ×100), and CD30 of variable intensities marked the activated immunoblasts (F. ×200). (G and H) The follicular dentritic meshwork stained by CD21 extended barely from the follicles, sparing the interfollicular zone intact (×100). (I-L) Markers of angioimmunoblastic T-cell lymphoma such as CD10 (I and J. ×200), Bcl-6 (K. ×200) and CXCL13 (L. ×200) didn't reveal any neoplastic cells (A-L. immunohistochemistry, Roche Benchmark XT, original magnification). (M) EBER was positive in the interfollicular areas (In situ hybridization, Ventana Benchmark, original magnification, ×400). (N) TCRβ-VJ2, TCRβ-DJ and TCRγ-VJ2 gene were rearranged (M, marker; 1, TCRβ-VJ1; 2, TCRβ-VJ2; 3, TCRβ-DJ; 4, TCRγ-VJ1; 5, TCRγ-VJ2).
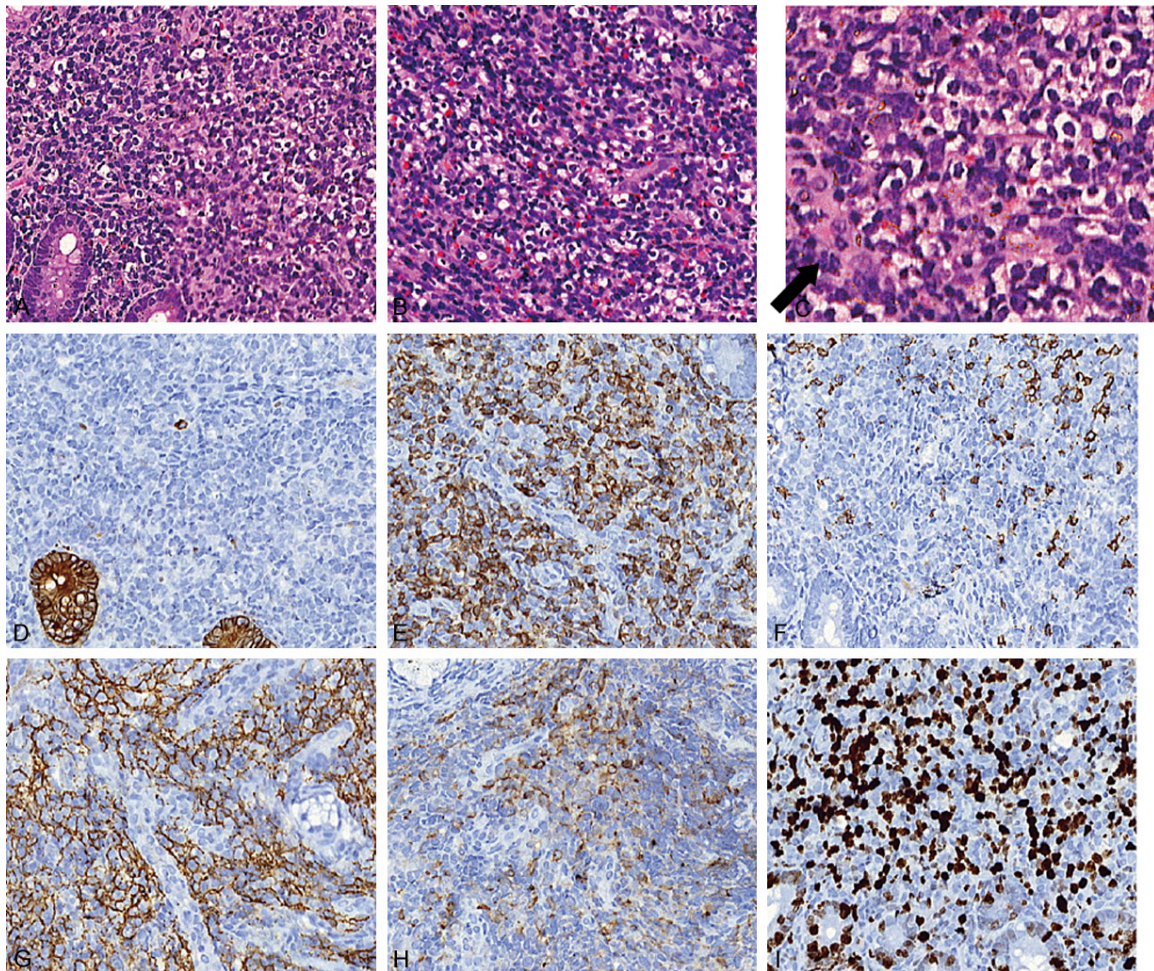
Figure 3. Morphology and immunophenotype of the duodenal bulb biopsy in the second admission. (A-C) The mucosa was infiltrated by polymorphous lymphoid cells, including clusters of clear-cytoplasm atypical lymphoid cells (A and B. HE, original magnification, ×200; C. HE, original magnification, ×400). Arborizing postcapillary high endothelial venules (HEVs) were conspicuous (arrow in C). (D) AE1/AE3 staining shows the remaining mucosal glands (×200). (E-I) Markers of CD3 (E. ×200), CD20 (F. ×200), CD21 (G. ×200) and CD10 (H. ×200) suggested angioimmunoblastic T-cell lymphoma. The proliferative index was approximately 40 percent (I. ×200) (E-I. immunohistochemistry, Roche Benchmark XT, original magnification).

zation of EBV EBER showed strong nuclear positive in 30%-40% lymphoid cells in the paracortical/interfollicular areas. T-cell clonality analysis by PCR demonstrated that TCRβ-VJ2, TCRβ-DJ and TCRγ-VJ2 genes were rearranged (**Figure 2M** and **2N**).

Morphology and immunophenotype of the duodenal bulb biopsy in the second admission

HE staining indicated the mucosal glands decreased and the mucosa was infiltrated by polymorphous lymphoid cells, including clusters

of clear-cytoplasm atypical lymphoid cells. The lymphoid cells with clear cytoplasm were prominent in the background of small lymphocytes, plasmacytes and eosinophils. HEVs were conspicuous (**Figure 3A-C**). Immunohistochemical staining shows the remaining mucosal glands by AE1/AE3. The markers (CD10, BCL6, CXCL13) of angioimmunoblastic T-cell lymphoma were well expressed, and the proliferative index was approximately 40 percent (**Figure 3D-I**).

Morphology, immunophenotype and genetics of the left axillary lymph node in the second admission

HE staining showed the architecture of the lymph node was effaced, replaced by a polymorphic infiltration of small-medium lymphocytes intermingled with histiocytes, immunoblasts and plasma cells. Atypical lymphocytes with broad and clear cytoplasm and arborizing postcapillary HEVs (HEVs) were prominent. The atypical lymphocytes were positive for CD3, CD8, CD10 and CXCL13, and negative for CD4 and CD20. The immunoblasts were positive CD30. CD21 highlighted the follicular dendritic cell meshwork around HEVs. The proliferation index was approximately 50 percent (**Figure 4A-L**). In situ hybridization of EBV EBER showed 40-50% lymphoid cells were strong nuclear positive. T-cell clonality analysis by PCR revealed TCRγ-VJ2 genes were rearranged (**Figure 4M** and **4N**).

Discussion

AITL occurs in the middle-aged and elderly, with an equal incidence in males and females. It involves lymph node, spleen, liver, skin and bone marrow (BM). Clinically, AITL presents with advanced stage disease, systemic symptoms, generalized lymphadenopathy, hepatosplenomegaly and polyclonal hypergammaglobulinemia. Other common clinical findings are skin rash, pleural effusion, arthritis and ascites. Laboratory findings include circulating immune complexes, cold agglutinins, with haemolytic anaemia, positive rheumatoid factor and anti-smooth muscle antibodies. By in situ hybridization, Epstein-Barr virus (EBV) has been detected in 80-96% of lymph nodes involved by the disease [5, 7].

The lymph node structure of AITL is usually destroyed. There are three major patterns of architectural changes of AITL. In pattern 1 (20% of cases), the normal structure is intact and the hyperplastic germinal centers are prominent. In Pattern 2 (30% of cases), normal architecture is lost, with occasional depleted follicles or "burned out" germinal centers. In pattern 3 (50% of cases), the normal structure is completely effaced, and no B-cell follicles are present [4, 8].

In AITL, a polymorphic infiltrate of small to medium-sized atypical lymphocytes admixed with immunoblasts, granulocytes, eosinophils, plasma cells, fibroblast-like dendritic cells, histiocytes, and epithelioid cells occupies the paracortical/interfollicular area. The atypical T cells characterized by round to irregular nuclear contours and broad, clear cytoplasm with distinct cell membranes. The proportion of the neoplastic cells varies greatly from small foci to large confluent sheets. Arborizing postcapillary HEVs are prominent feature of AITL, which are numerous and may be found outside the lymph nodes in the perinodal infiltrate. Meshworks of follicular dendritic cells (FDCs) outside the residual follicles and abutting the HEVs are prominent when stained with CD21 [7].

The neoplastic T cells are CD4 positive in most cases, although CD8 positive T cells may constitute the majority in some cases. CD21 and/ or CD23 highlight the disorganized and largely expanded meshworks of FDCs. FDCs usually surround HEVs in most cases and is often associated with B-cell follicles in early histologic stages of the disease. The expression of CD10, BCL6, CXCL13 and PD1 represents an important adjunct in the diagnosis of AITL and provides further evidence that AITL derives from follicular helper T lymphocytes (TFH) [8, 9]. It is not uncommon to find that only the neoplastic T cells embedded in FDC meshworks express TFH-associated markers, which suggests that the germinal-center microenvironment is necessary for the expression of TFH phenotype. The expression of EBV LMP1 can be demonstrated in the B cells of 30% to 50% of cases. Immunoblasts usually express CD30 and B cell markers. EBV infects transformed B cells in most cases, and the infected B cells may account to 1 in 10 to 1 in 500 B cells in lymph nodes. Despite the prevalence of EBV in AITL, it is currently thought that its presence is not causitive, because it most likely reflects the underlying immunodeficiency of AITL [10].
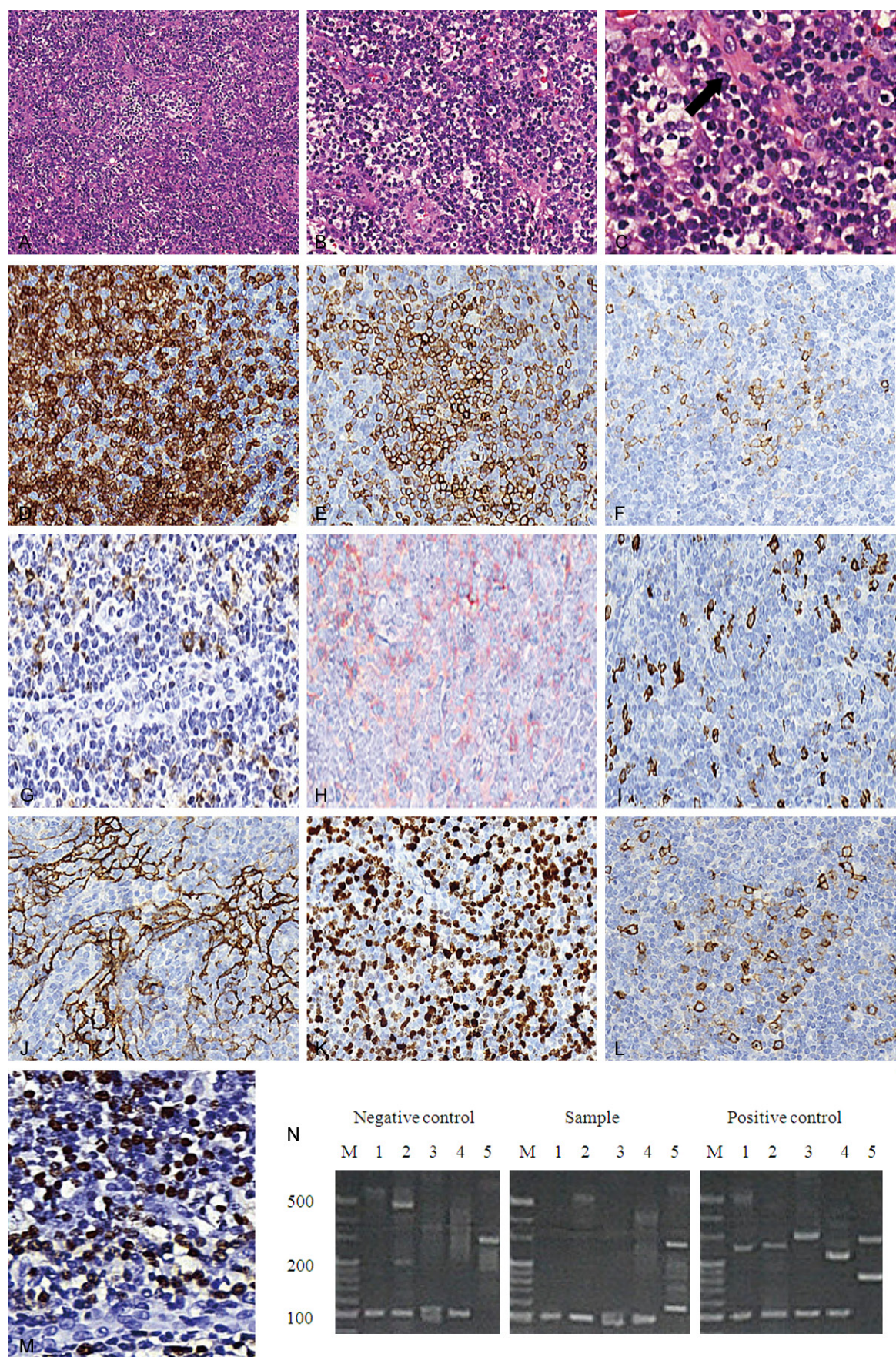
Figure 4. Morphology, immunophenotype and genetics of the left axillary lymph node in the second admission. (A-C) The architecture of the lymph node was effaced and replaced by a polymorphic infiltration of small-medium lymphocytes intermingled with histiocytes, immunoblasts and plasma cells. The atypical lymphoid cells were characterized by broad and clear cytoplasm (A. HE, original magnification, ×100; B. original magnification, ×200; C. HE, original magnification, ×400). Arborizing postcapillary high endothelial venules (HEVs) (arrow in C) were prominent. (D-I) The atypical lymphocytes were positive for CD3 (D. ×200), CD8 (E. ×200), CD10 (F. ×200) and CXCL13 (G. ×200) and negative for CD4 (H. ×200) and CD20 (I. ×200). (J) CD21 highlighted the follicular dendritic cell enveloping HEVs (×200). (K) The proliferation index of the atypical lymphocytes was approximately 50 percent (×200). (L) The scattered immunoblasts were positive for CD30 (×200) (D-L, immunohistochemistry, Roche Benchmark XT, original magnification). (M) Detection of EBER was positive (In situ hybridization, Ventana Benchmark, original magnification, ×400). (N) TCRγ-VJ2 gene was rearranged (M, marker; 1. TCRβ-VJ1; 2. TCRβ-VJ2; 3. TCRβ-DJ; 4. TCRγ-VJ1; 5. TCRγ-VJ2).

The tumor cells of 75% AITL cases are monoclonal with TCR arrangement. About 11%-25% of AITL cases lack either clonal TCR or cytogenetic abnormalities. These cases may represent early stages of a lymphoma with a minor oligoclonal T-cell population. In approximately 25%-30% of cases, rearrangements of the immunogolobulin heavy-chain (IGH) or light-chain genes may coexist, which is thought to manifest the clonal expansion of EBV-infected B cells. Gene-expression studies have shown that AITL derived from TFH cells, and that genes related to cell morphology, intracellular signaling, and promoting angiogenesis such as VEGF are overexpressed in AITL [7]. The treatment of AITL includes chemotherapy, radiotherapy, clinical trial, allogeneic stem cell transplant or autologous stem cell rescue [1, 11].

Our case is an elderly man with a 3-month history on his first admission, and his clinical manifestations reminded us of AITL. However, both the morphology and immunophenotype suggested reactive hyperplasia predominated by paracortical hyperplasia. EBER detection result revealed the infection of EBV. TCRβ-VJ2, TCRβ-DJ and TCRγ-VJ2 genes were rearranged. After using ganciclovir and dexamethasone, the enlarged superficial lymph nodes waned. The two drugs worked well whenever the patient suffered from recurrent attacks during the early one month after the first hospitalization. About 4 months after onset, the patient's condition deteriorated with extensive systemic symptoms and didn't respond to antiviral therapy. The patient re-hospitalized, computerized tomography and gastroscopy revealed multiple lesions. Morphological, immunophenotypic and genetic findings of both the ulcers in duodenal bulb and a superficial lymph node resulted in the diagnosis of AITL. Although received the chemotherapy of COP immediately, the patient died of respiratory and circulatory failure caused by AITL eventually. Our patient's condition progressed rapidly, only lasting about 6 months from onset to death. In the early 4 months, the pathological characteristic was reactive hyperplasia predominated by paracortical hyperplasia. The few expansions of FDC meshworks from the germinal center suggested a possibility of very early stage of AITL.

In our case, the rearrangements of three TCR genes of the first biopsy seem to be confusing. For AITL, there is a considerable morphologic overlap with paracortical hyperplasia. Paracortical hyperplasia is usually associated with viral infections or with a hyperimmune reaction secondary to an autoimmune disease, with preservation of the lymph node architecture and without aberrant FDC proliferation. In the paracortical area, there is a polymorphous infiltrate of small to medium lymphocytes without atypia, numerous plasma cells, immunoblasts, histiocytes. Immunophenotypical analysis reveals a mixed CD4-CD8 population with scattered CD20-positive cells, and CD10/BCL6-positive cells are confined to the follicles. No TCR rearrangements are identified [12]. Cytogenetic studies have demonstrated that clones can appear and disappear and new clones can emerge over time in AITL. AITL most likely starts as a deregulated immune response to antigenic stimulation, which may lead to multiple proliferating clones (oligoclones). Some of the clones may regress spontaneously, and some may progress and transform into malignant clones. Although the current belief is that AITL generally starts de novo as a peripheral T-cell lymphoma, it is probable that in some cases AITL represents a continuum whereby atypical and oligoclonal cell proliferations correspond to a precursor or preneoplastic lesion before the development of an over malignant lymphoma

[13]. In our view, our patient's immune system deregulated after the infection of EBV. Subsequently, the lymphoid tissue experienced an atypical oligoclonal cell proliferations and progressed to overt AITL within 4 months. The patient died of respiratory and circulatory failure caused by AITL only 6 months later from the onset.

There are 14-20% PTCL, NOS cases expressing profile of AITL and some showing proliferation of FDCs, which suggests the possibility of AITL progressing into PTCL, NOS [14]. Some genes involved in epigenetic gene regulation, such as TET2, DNMT3A and IDH has been demonstrated in AITL. RHOA gene mutations have been identified in about 70% of AITL cases. Mutations in TET2, RHOA and DNMT3A genes have been reported also in a subgroup of PTCL, NOS, further supporting the concept of tumor cell-rich AITL subtype [15-17]. The differential diagnosis between AITL and PTCL, NOS can be complicated, because the atypical tumor cells, the background inflammatory cells, and the HEVs can be present in both entities. The immunophenotype is helpful in the differential diagnosis [14].

The HRS-like cells in AITL may resemble Hodgkin's lymphoma occasionally. These cells express CD30 and CD20, and harbor EBV in most cases (EBER and LMP-1). In another hand, many AITL cases show minimal cytological atypia of cells, the distinction from classical Hodgkin's lymphoma may be difficult. The rearrangements of the TCR genes are helpful to diagnose AITL [7].

Because of the frequent occurrence of scattered B blasts in AITL, T-cell/histiocyte-rich large B-cell lymphoma should be included in the differential diagnosis. In T-cell/histiocyte-rich B-cell lymphoma, the background infiltrate is not as polymorphic as in AITL, expanded meshworks of FDC do not occur, and the B blasts are CD30- and EBV- in general. Molecular biology analysis shows monoclonal IGH rearrangements, and no TCR gene rearrangements are identified [7].

In conclusion, our case showed a morphology feature of lymphoid hyperplasia predominated by paracortical hyperplasia with rearrangements of TCR genes, which may be an early stage of AITL. The lymphoid hyperplasia progressed to overt AITL rapidly, which made the patient died of complications caused by AITL within only 6 months. It is possible that there is a continuous process of atypical and oligoclonal cell proliferations corresponding to a precursor or preneoplastic lesion developing to an over malignant lymphoma in some cases of AITL.

Disclosure of conflict of interest

None.

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