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Chapter 3

T- and NK/T-Cell Leukemia in East Asia

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1. Introduction

The relative frequency of lymphoma types varies in different geographic region. Human T-cell lymphotropic virus type I (HTLV-I) infection is endemic in south-western Japan which leads to a high frequency of adult T-cell leukemia/lymphoma (ATLL). As compared to the West, East Asian countries have higher relative frequencies of T- and natural killer (NK)-cell lymphomas, which account for about 15-20% of non-Hodgkin lymphoma after excluding ATLL in some Japanese series [1-5]. Accordingly, a higher frequency of T- and NK/T-cell leukemia would be expected in East Asia. As compared to B-cell lymphomas, T- and NK/T-cell neoplasms more frequently occur at extranodal locations, and may occasionally present as leukemia, either with or without concomitant lymphoma.

There are around 20 entities and variants of T- and NK/T-cell neoplasms in the 4th edition of World Health Organization (WHO) classification of lymphoid neoplasms [6]. Table 1 lists the T- and NK/T-cell neoplasms which may have leukemic presentation. The first category comprises entities that are predominantly leukemic including T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGLL) and aggressive NK-cell leukemia (ANKL). The second category includes neoplasms that frequently present with concurrent lymphoma and leukemia such as T lymphoblastic leukemia/lymphoma (T-LBL), ATLL and Sézary syndrome. The third category includes T-cell lymphoma with secondary peripheral blood involvement such as unspecified peripheral T-cell lymphoma (PTCL-NOS) progressing to a leukemic phase and very rarely extranodal NK/T-cell lymphoma (ENKTL) with peripheral blood involvement, which might overlap with ANKL [7]. In the East Asian region other than Japan, ATLL is extremely rare and the discussion on this entity is covered in the other chapters. Sézary syndrome is extremely rare in this region as well. Accordingly we will not discuss these two entities in this chapter.

A. Predominantly leukemic
1. T-cell prolymphocytic leukemia (T-PLL)
2. T-cell large granular lymphocytic leukemia (T-LGLL)
3. Aggressive NK-cell leukemia (ANKL)
B. Concurrent lymphoma/leukemia
1. T lymphoblastic lymphoma/leukemia (T-LBL)
2. Adult T-cell lymphoma/leukemia (ATLL)
3. Sézary syndrome
C. Lymphoma with secondary peripheral blood involvement
1. Peripheral T-cell lymphoma with peripheral blood involvement
2. Extranodal NK/T-cell lymphoma with peripheral blood involvement

Table 1. T- and NK/T-cell neoplasms with leukemic presentation.

There are very few reports systemically reviewing the whole spectrum of T- and NK/T-cell neoplasms with leukemic presentation in the East Asia. In a prospective study of chronic lymphoproliferative disorders in Hong Kong in an 18-month period from January 1995 to June 1996, there were a total of 34 cases of chronic lymphoproliferative disorder, estimated at 0.54 case per million populations per year, as compared to 245 new cases of acute myeloid leukemia in the same study period [8]. Of these 34 cases, the majority were B-cell neoplasms with the remaining 3 (9%) cases being T-cell leukemias including one case each of T-PLL, Sézary syndrome and T-LGLL [8]. In our recent retrospective study of 718 consecutive patients with lymphoid neoplasms in a single institution in Taiwan, the frequency of T- and NK/T-cell neoplasms with leukemic presentation was 13.1% (18 of 137 patients) [9]. Our study showed that cases with concurrent lymphoma, higher absolute leukemic cell counts, and elevated lactate dehydrogenase level carried a poorer prognosis. The survival of patients with leukemic presentation was dichotomous, with a very poor prognosis for patients with T-LBL, T-PLL, ANKL, ATLL in acute phase, and PTCL-NOS; while those with T-LGLL and ATLL in chronic phase had a favorable outcome.

Table 2 summarizes the relative frequency of various T- and NK/T-cell leukemia in different countries in the East Asia [1,4,9]. As mentioned previously, T- and NK/T-cell neoplasms account for 15-20% of lymphomas in this region. The relative frequency of T-LBL among T-cell neoplasms is low in Taiwan and Japan at less than 10%, but it is high at 23.77% (208 of 875 cases) in Korea, which is partly due to the inclusion of all lymphoid neoplasms including T-cell acute lymphoblastic leukemia in that Korean study [4]. T-PLL is very rare in all 3 countries with a relative frequency of less than 1% among T-cell neoplasms. T-LGLL and ANKL are also rare with a frequency of less than 1% except for a higher frequency of the former in Taiwan and the latter in Korea, respectively. The higher relative frequency of T-LGLL in our series in Taiwan is probably due to a higher interest of this entity in our laboratory with confirmation of suspicious cases by T-cell receptor (TCR) gene rearrangement and/or flow cytometry immunophenotyping (aberrancy in T-cell antigen expression or clonal by flow

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cytometric TCR-Vβ repertoire analysis) [10]. While in other pathology laboratories, such cases might either be unrecognized or diagnosed solely by hematologists without marrow trephine biopsy and thus not being enrolled in the pathology files for lymphoma analysis. In the following sections, we will discuss each specific T- and NK/T-cell neoplasm.

	Taiwan [9]	Japan-1A [1]	Japan-1B [1]	Japan-2 [5]	Korea [4]
T-cell/total neoplasms (%)	137/718 (19.08%)	796/3,194 (24.92%)	558/2,956 (18.88%)	287/1,552 (18.49%)	875/5,318 (16.45%)
T-LBL	2.92% (n=4)	6.91% (n=55)	9.86% (n=55)	6.62% (n=19)	23.77% (n=208)
T-PLL	0.73% (n=1)	0.25% (n=2)	0.36% (n=2)	0.35% (n=1)	0.57% (n=5)
T-LGL leukemia	5.10% (n=7)	0.25% (n=2)	0.36% (n=2)	-	0.23% (n=2)
ANKL	0.73% (n=1)	0.38% (n=3)	0.54% (n=3)	0.70% (n=2)	3.31% (n=29)
ATLL	2.92% (n=4)	29.90% (n=238)	Excluded	14.29% (n=41)	0.11% (n=1)

*Data of various T- and NK-cell neoplasms are presented as percentage (case number) among the total number of T- and NK-cell neoplasms in each country.

Columns Japan-1A and -1B are from the same reference with exclusion of ATLL cases in the column of Japan-1B.

Table 2. Relative frequency of various T- and NK/T-cell leukemia among T-cell neoplasms in representative East Asian countries.

2. T Lymphoblastic Leukemia/Lymphoma (T-LBL)

T-LBL is a rare neoplasm occurring more commonly in adolescents, accounting for 1-4% among malignant lymphomas in East Asia [1,2,4,5,9]. Patients with T-LBL usually present with a very high leukemic cell count (frequently over 150,000/μL), and often with a large mediastinal mass [9]. The diagnosis is often straightforward with typical clinical features and numerous blasts in the peripheral blood with a fine chromatin pattern and irregular nuclear contours (Fig. 1A). Phenotypically, the neoplastic cells express cytoplasmic but not surface CD3; and they frequently co-express CD4 and CD8. The most important and reliable immature cell marker is terminal deoxynucleotidyl transferase (TdT), which could be used either in immunohistochemistry or flow cytometry [11]. The other immature markers are CD1a, CD34 and CD99 [12,13]. Immunohistochemically, occasional cases of T-LBL may not express TdT, but instead, express CD34 and/or CD99 [14]. The immunophenotype of T-LBL and T-cell acute lymphoblastic leukemia are identical but differ in frequency, with a higher rate of later phases of development (cortical or mature immunophenotype) in T-LBL, which is probably reflecting the higher rate (> 90%) of mediastinal tumors [15].

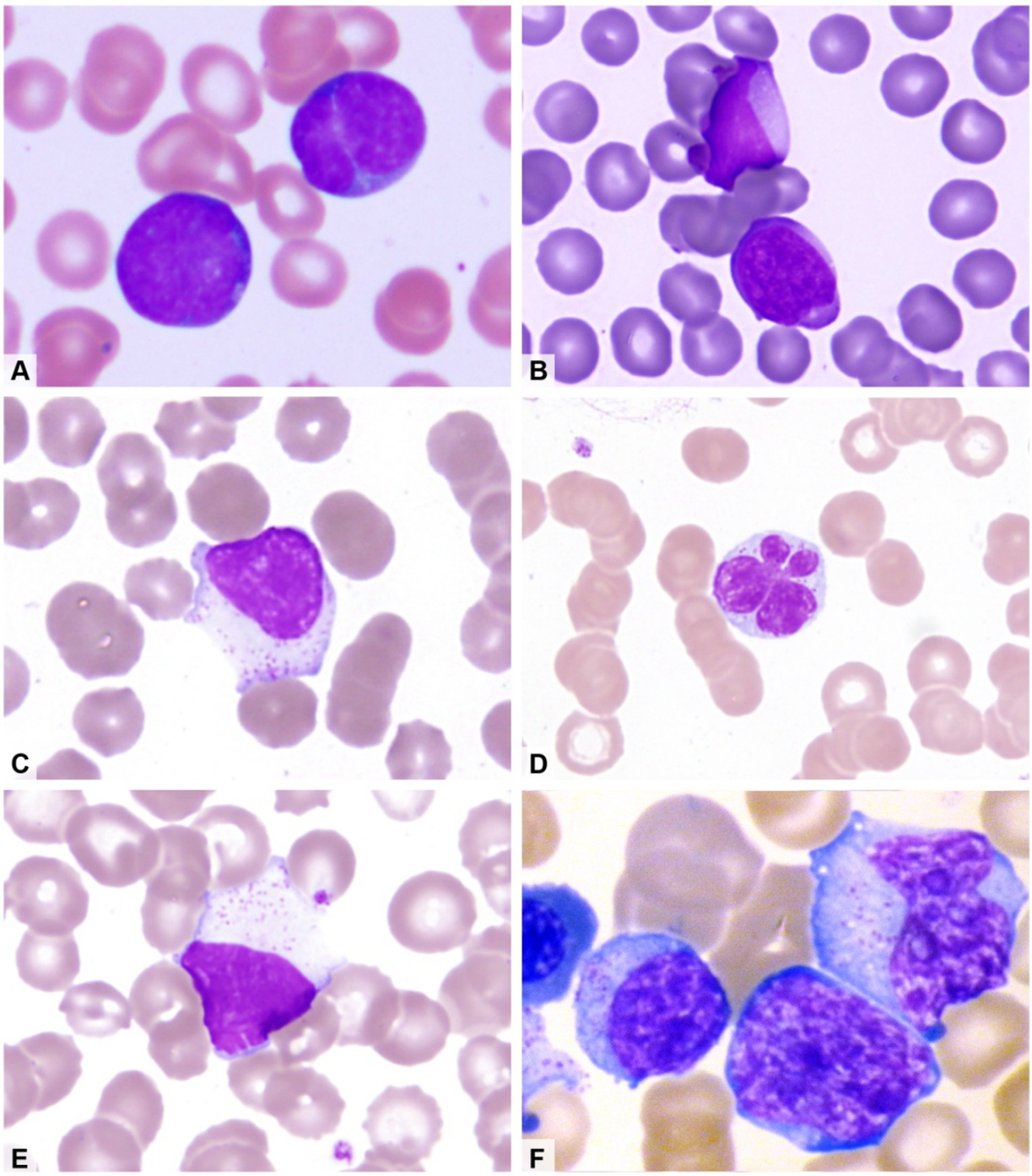

Figure 1. Photomicrographs of representative cases in the peripheral blood smear of A) T-LBL with indented nuclei, B) T-PLL of small cell variant without nucleoli, C) T-LGLL with usual LGL morphology containing azurophilic cytoplasmic granules, D) T-LGLL with atypical morphology characterized by irregular nuclear contours resembling a flower, E) reactive NK lymphocytosis and F), ANKL.

3. T-cell Prolymphocytic Leukemia (T-PLL)

T-PLL is rare, representing around 2% of mature lymphocytic leukemia in adults over the age of 30 in the West with a median age of 65 [16]. The main disease features are splenomegaly, lymphadenopathy, hepatomegaly, skin lesions, and a high leukocyte count comprising small to medium-sized nucleolated prolymphocytes with cytoplasmic protrusions or blebs but devoid of granules (Fig. 1B). Small cell variant with small, less typical cells and an indistinct nucleolus has been recognized in 20% cases [16]. T-PLLs account for less than 1% of T- and NK-cell lymphomas in East Asia. The clinical manifestations and immunophenotype of T-PLL in Japan are similar to those of the Western cases [17-19]. However, there is a significantly higher frequency of tumor cells in Japanese cases expressing HLA-DR than that of Western cases [17]. Chromosome 14q11 abnormality and trisomy 8q, which are frequently seen in T-PLL of Western countries (70-80%), are not common in Japan [18]. Furthermore, a substantial number of T-PLL cases in Japan shows abnormal expression of TCL1A, probably due to rearrangement of *TCL1* gene, which may serve as a useful marker for diagnosing T-PLL [19]. In contrast to the aggressive clinical courses observed in Western T-PLL patients, Kameoka et al. reported that 6 out of 13 Japanese patients experienced an indolent course. Interestingly, the clinical course closely correlated with morphology; 86% cases of typical morphology were aggressive, whereas 83% of small-cell variant were indolent [17]. Studies on more cases are needed to see if Japanese T-PLL constitutes a variant of T-PLL. In East Asia countries other than Japan, there are only scanty reports on T-PLL, either included in a small case series or as a single case report [9, 20].

4. T-cell Large Granular Lymphocytic Leukemia (T-LGLL)

Large granular lymphocytes (LGLs) are medium to large-sized lymphocytes with azurophilic cytoplasmic granules that normally comprise 10-15% of the peripheral blood mononuclear cells (PBMCs) and serve as the main effector cells of cell-mediated cytotoxicity. The majority (85%) of these LGLs are NK-cells with the remaining minority being CD8-positive cytotoxic T-cells [21]. LGL lymphoproliferation may be reactive or neoplastic; and reactive LGL lymphoproliferation occurs most commonly in patients with viral infection such as cytomegalovirus infection and infectious mononucleosis, autoimmune disease or an underlying malignancy [10,22]. In the 2008 WHO classification scheme, T-LGLL is defined as a heterogeneous disorder characterized by a persistent (> 6 months) increase in the number of LGL in the peripheral blood, usually between 2-20 $x10^9$/L, without a clearly identified cause [23]. In cases with absolute LGL count less than 2 $x10^9$/L, the diagnosis of T-LGLL could be established if clonal T-cell lymphoproliferation is confirmed, either by TCR gene rearrangement and/or flow cytometry immunophenotyping (aberrancy in T-cell antigen expression or clonal by flow cytometric TCR-Vβ repertoire analysis) [10,24-28]. In most instances, the morphology of the leukemic cells in T-LGLL is indistinguishable from that of the normal LGLs (Fig. 1C), with the exception of

extremely rare examples showing markedly pleomorphic nuclei indicating a neoplastic lymphoproliferation (Fig. 1D) [29].

A recent study led by Prof. Kwong YL from Hong Kong characterized 22 Chinese T-LGLL patients in his institution in Hong Kong and found that the most important indication for treatment of their patients was anemia, in contrast to neutropenia in Western patients [30]. Compiling their cases with 88 Asian patients in comparison with 272 Western patients identified from the literature, they found that Asian patients had more frequent anemia (66/110, 60% vs. 113/240, 47%; p=0.044), attributable to a much higher incidence of pure red cell aplasia (PRCA; 52/110, 47% vs. 6/143, 4%; p<0.001) [30]. On the other hand, Western patients presented more frequently with neutropenia (146/235, 62% vs. 33/110, 30%; p<0.001) and splenomegaly (99/246, 40% vs. 16/110, 15%; p<0.001) [30]. Notably, Western patients were about eight to ten times more likely than Asian patients to have rheumatoid arthritis (73/272, 27% vs. 4/106, 4%; p<0.001) and recurrent infections (81/272, 30% vs. 3/107, 3%; p<0.001) [30]. They concluded that different disease mechanisms might be involved in T-LGLL in different populations.

Table 3 summarizes the laboratory and clinical findings of T-LGLL in Taiwan, Hong Kong and the West. Our very recent study of 17 Taiwanese patients with T-LGLL showed a higher mean hemoglobin level (10.5 vs. 8.1 g/dL) and a lower rate of anemia (8/17, 47% vs. 17/22, 77%; p=0.028) as compared to the Chinese patients in Hong Kong; while the frequency of anemia in our patients was similar to that (113/227, 49.8%) of the Western patients (p= 0.988) [10]. Because anemia was not a major problem in our patients and thus bone marrow aspiration/biopsy was performed only in 8 patients. Even so, our cohort of patients showed a lower rate of PRCA as compared to the Hong Kong series (2/8, 25% vs. 17/22, 68%; p=0.035). Interestingly, in our small series of patients, the frequency of PRCA was higher than that (6/143, 4.2%) of the Western patients (p= 0.010). There were no other statistically significant laboratory and clinical parameters between Taiwanese vs. Hong Kong Chinese or Taiwanese vs. Western T-LGLL patients. More studies from East Asian patients are warranted to see if there is a genuine ethnic difference in patients with T-LGLL, particularly in terms of the frequency of anemia and PRCA.

Apart from arising as *de novo* neoplasms, T-LGLL may arise after hematopoietic stem cell or solid organ transplantation [31-38]. Notably, most of the reported cases of T-LGLL after hematopoietic stem cell transplantation are from East Asia. Prof. Kwong's group from Hong Kong recently reported the largest series of 7 such patients who did not have cytopenia, autoimmune phenomenon or organ infiltration, features typical of *de novo* T-LGLL [39]. Excluding 1 patient died from cerebral relapse of the original lymphoma, the remaining 6 patients had remained asymptomatic with stable LGL counts for long periods not requiring any specific treatment. T-LGLL occurring after hematopoietic stem cell transplantation seems to be distinct from *de novo* T-LGLL and may have a different pathogenesis and clinical course.

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	Taiwan (n=17)	HK (n=22)	West* (n=272)	*P (Taiwan vs. HK)*	*P (Taiwan vs. West)*
Sex					
Male	12	14	125		
Female	5	8	146	0.668	0.050
Age (mean ± SE of the mean, years)	62.1 ± 4.1	52.3 ± 3.2		0.121	
Hemoglobin					
Mean ± SE of the mean (g/dL)	10.5 ± 0.7	8.1 ± 0.7		0.019	
Low(<10 g/dL)	8	17	113	0.028	0.988
Neutrophil count					
Mean ± SE of the mean ($x10^9$/L)	2.7 ± 0.5	3.4 ± 1.0		0.479	
Low (<1.5$x10^9$/L)	8	8	146	0.523	0.218
LGL count					
Mean ± SE of the mean ($x10^9$/L)	4.5 ± 1.2	4.8 ± 0.7		0.523	
High (>2$x10^9$/L)	11	14	133	0.980	0.110
Platelet count					
Mean ± SE of the mean ($x10^9$/L)	223 ± 31	204 ± 28		0.989	
Low (<150$x10^9$/L)	7	5	47	0.337	0.075
Hepatomegaly					
Present	3	5	35		
Absent	7	17	211	0.659	0.169
Splenomegaly					
Present	2	8	99		
Absent	8	14	147	0.335	0.199
Pure red cell aplasia					
Present	2	15	6		
Absent	6	7	137	0.035	0.010
Rheumatoid arthritis					
Present	1	0	73		
Absent	13	22	199	0.203	0.100
Autoimmune phenomena					
Present	0	1	5		
Absent	14	21	267	0.418	0.608

Data from the Western series is based on the report by Prof. Kwong et al [30].

Abbreviation: HK, Hong Kong; SE, standard error.

The statistical analyses of data were performed by student t test or chi square test where appropriate (SPSS, Chicago, IL, USA.)

Table 3. Comparison of T-LGLL in Hong Kong, China, Taiwan and West

In patients with solid organ transplantation clonal T-LGL proliferation seems to be not uncommon. Sabnani et al. found that 71% (10/14) cardiac and 44% (4/9) renal transplant patients had clonal expansion of T-LGL cells but without evidence of either allograft rejection or a viral syndrome. Constitutional symptoms were present in 30% of these patients. Anemia was seen in 75% of renal transplant and 10% of cardiac transplant patients, but none of these patients had significant neutropenia. They believe that this monoclonality is not a true form of post-transplant lymphoproliferative disorder. Constant antigenic stimulus such as a cytomegalovirus reactivation may be the underlying etiology of clonal T-LGL expansion and may contribute to cytopenias and fatigue seen in transplant patients [38].

5. Aggressive NK-cell Leukemia (ANKL)

ANKL is a systemic proliferation of NK-cells, almost always associated with Epstein-Bar virus (EBV) and an aggressive clinical course [40]. This catastrophic disease is observed almost exclusively in Asian patients who are usually very ill on presentation, with pyrexia, jaundice, pancytopenia, skin infiltration, lymphadenopathy and hepatosplenomegaly [40,41]. The most commonly involved sites are peripheral blood, bone marrow, liver and spleen. The leukemic cells may show a wide range of appearance from normal-looking LGL as seen in reactive NK lymphocytosis (Fig. 1E) to atypical (e.g. irregular nuclear foldings, very large size) or immature (e.g. open chromatin, distinct nucleoli) morphological features (Fig. 1F) even in an individual case [42]. The number of neoplastic cells in the peripheral blood and bone marrow can be limited or numerous, from less than 5% to greater than 80% of lymphocytes [42]. Furthermore, there are cases with overlapping features with ENKTL [43,44]. Accordingly, ANKL has also been called aggressive NK-cell lymphoma/leukemia; however, patients with ANKL are younger and the incidence of skin involvement is significantly lower than ENKTL. It is currently unclear whether ANKL is the leukemic counterpart of ENKTL [40].

Phenotypically, the leukemic cells of ANKL in a Japanese series of 22 cases were characterized by the expression of CD2, cytoplasmic CD3, CD56 and HLA-DR with frequent expression of CD7 (14/19 cases, 74%), CD8 and CD16. They did not express surface CD3, CD4, CD5 or CD25 [45]. Interestingly, in a Korean series of 20 cases, CD7 antigen loss was detected in 10 patients (50%) [46]. The Korean investigators claimed that, in conjunction with the cytogenetic findings, this characteristic immunophenotypic finding could serve as a reliable marker for the timely diagnosis in 75% of ANKL [46]. However, there were no statistically significant difference in the clinical or laboratory parameters between the CD7+ and the CD7- ANKL patients. To our knowledge, there are only 2 reports of ANKL from Taiwan, and the leukemic cells in 6 of 7 (86%) cases expressed CD7 [47,48]. No statistically significant difference on CD7 expression was identified between ANKL cases in Taiwan, Japan or Korea (Fishers' exact test).

The great majority of ANKL is associated with EBV-- 85% (11/13) in a Japanese series, 88% (14/16) in a Korean series and 71% (5/7) compiled from the two reports from Tai-

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wan [45,47-49]. The EBV infection in ANKL is an episomal form, indicating a clonal integration into leukemic cells. Prof. Ko et al. compared the clinicopathological characteristics of EBV-negative ANKL patients with those of EBV-positive ANKL patients in Korea and reviewed the literature for reports on EBV-negative ANKL cases. They found that EBV-negative and EBV-positive ANKL patients had similar clinical and pathological characteristics, but EBV-negative patients had a longer survival than EBV-positive patients (11.5 vs. 1.5 months, respectively). EBV-negative patients achieved complete remission, but tumors often relapsed after a short interval, indicating a less aggressive clinical course than EBV-positive ANKL [49].

6. Mature T- and NK/T-cell lymphoma with peripheral blood involvement

The most common T-cell lymphoma with peripheral blood involvement is ATLL and is discussed in the previous chapters. The other T-cell lymphoma with peripheral blood involvement is Sézary syndrome, which is characterized by the triad of erythroderma, generalized lymphadenopathy and the presence of clonally related T-cells with cerebriform nuclei (Sézary cells) in skin, lymph nodes and peripheral blood [50]. Very rarely, PTCL-NOS and ENKTL may progress to bone marrow and peripheral blood involvement, usually in the terminal stage of disease [7,9].

7. Conclusion

In this chapter, we review and analyze various types of T- and NK/T-cell leukemias in the East Asia. Several of these rare neoplasms have not been reported in some East Asian countries yet. Interestingly, there are certain features in some entities, such as T-LGLL, that are distinct from the Western population. More epidemiological, clinicopathological and genetic studies on these rare neoplasms are warranted.

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References

[1] Lymphoma Study Group of Japanese Pathologists. The world health organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. Pathol Int. 2000;50:696-702.

[2] Chuang SS, Lin CN, Li CY. Malignant lymphoma in southern Taiwan according to the revised European-American classification of lymphoid neoplasms. Cancer. 2000;89:1586-1592.

[3] Chuang SS. Significant increase in the relative frequency of follicular lymphoma in Taiwan in the early 21st century. J Clin Pathol. 2008;61:879-880.

[4] Yoon SO, Suh C, Lee DH, Chi HS, Park CJ, Jang SS, et al. Distribution of lymphoid neoplasms in the Republic of Korea: analysis of 5318 cases according to the World Health Organization classification. Am J Hematol. 2010;85:760-764.

[5] Miura Y, Fukuhara N, Yamamoto J, Kohata K, Ishizawa K, Ichinohasama R, et al. Clinicopathological features of malignant lymphoma in Japan: the Miyagi Study. Tohoku J Exp Med. 2011;224:151-160.

[6] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., ed. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC; 2008.

[7] Rezk SA, Huang Q. Extranodal NK/T-cell lymphoma, nasal type extensively involving the bone marrow. Int J Clin Exp Pathol. 2011;4:713-717.

[8] Chan LC, Lam CK, Yeung TC, Chu RW, Ng M, Chow EY, et al. The spectrum of chronic lymphoproliferative disorders in Hong Kong. A prospective study. Leukemia. 1997;11:1964-1972.

[9] Chang ST, Hsieh YC, Kuo SY, Lu CL, Chu JS, Chuang SS. The spectrum of T-cell and natural killer/T-cell neoplasms with leukaemic presentation in a single institution in Taiwan. Int J Lab Hematol. 2012;34:422-426.

[10] Hsieh YC, Chang ST, Huang WT, Kuo SY, Chiang TA, Chuang SS. A Comparative Study of Flow Cytometric T-cell Receptor Vβ Repertoire and T-cell Receptor Gene Rearrangement in the Diagnosis of Large Granular Lymphocytic Lymphoproliferation. Int J Lab Hematol. 2012 in press.

[11] Suzumiya J, Ohshima K, Kikuchi M, Takeshita M, Akamatsu M, Tashiro K. Terminal deoxynucleotidyl transferase staining of malignant lymphomas in paraffin sections: a useful method for the diagnosis of lymphoblastic lymphoma. J Pathol. 1997;182:86-91.

[12] Pui CH, Hancock ML, Head DR, Rivera GK, Look AT, Sandlund JT, et al. Clinical significance of CD34 expression in childhood acute lymphoblastic leukemia. Blood. 1993;82:889-894.

[13] Robertson PB, Neiman RS, Worapongpaiboon S, John K, Orazi A. 013 (CD99) positivity in hematologic proliferations correlates with TdT positivity. Mod Pathol. 1997;10:277-282.

[14] Terada T. TDT (-), KIT (+), CD34 (+), CD99 (+) precursor T lymphoblastic leukemia/lymphoma. Int J Clin Exp Pathol. 2012;5:167-170.

[15] Hoelzer D, Gokbuget N. T-cell lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia: a separate entity? Clin Lymphoma Myeloma. 2009;9 Suppl 3:S214-221.

[16] Matutes E, Brito-Babapulle V, Swansbury J, Ellis J, Morilla R, Dearden C, et al. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. Blood. 1991;78:3269-3274.

[17] Kameoka J, Takahashi N, Noji H, Murai K, Tajima K, Kameoka Y, et al. T-cell prolymphocytic leukemia in Japan: is it a variant? Int J Hematol. 2012;95:660-667.

[18] Kojima K, Kobayashi H, Imoto S, Nakagawa T, Matsui T, Kawachi Y, et al. 14q11 abnormality and trisomy 8q are not common in Japanese T-cell prolymphocytic leukemia. Int J Hematol. 1998;68:291-296.

[19] Yokohama A, Saitoh A, Nakahashi H, Mitsui T, Koiso H, Kim Y, et al. TCL1A gene involvement in T-cell prolymphocytic leukemia in Japanese patients. Int J Hematol. 2102;95:77-85.

[20] Jeong KH, Lew BL, Sim WY. Generalized leukaemia cutis from a small cell variant of T-cell prolymphocytic leukaemia presenting with exfoliative dermatitis. Acta Derm Venereol. 2009;89:509-512.

[21] Sokol L, Loughran TP, Jr. Large granular lymphocyte leukemia. Oncologist. 2006;11:263-273.

[22] O'Malley DP. T-cell large granular leukemia and related proliferations. Am J Clin Pathol. 2007;127:850-859.

[23] Chan WC, Foucar K, Morice WG, Catovsky D. T-cell large granular lymphocytic leukemia. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., ed. WHO classification of tumours of haemtopoietic and lymphoid tissues. Lyon: IARC; 2008:272-273.

[24] Lima M, Almeida J, Santos AH, dos Anjos Teixeira M, Alguero MC, Queirós ML, et al. Immunophenotypic analysis of the TCR-Vbeta repertoire in 98 persistent expansions of CD3(+)/TCR-alphabeta(+) large granular lymphocytes: utility in assessing clonality and insights into the pathogenesis of the disease. Am J Pathol. 2001;159:1861-1868.

[25] Morice WG, Kimlinger T, Katzmann JA, Lust JA, Heimgartner PJ, Halling KC, et al. Flow cytometric assessment of TCR-Vbeta expression in the evaluation of peripheral blood involvement by T-cell lymphoproliferative disorders: a comparison with conventional T-cell immunophenotyping and molecular genetic techniques. Am J Clin Pathol. 2004;121:373-383.

[26] Feng B, Jorgensen JL, Hu Y, Medeiros LJ, Wang SA. TCR-Vbeta flow cytometric analysis of peripheral blood for assessing clonality and disease burden in patients with T cell large granular lymphocyte leukaemia. J Clin Pathol. 2010;63:141-146.

[27] Bareau B, Rey J, Hamidou M, Donadieu J, Morcet J, Reman O, et al. Analysis of a French cohort of patients with large granular lymphocyte leukemia: a report on 229 cases. Haematologica. 2010;95:1534-1541.

[28] Lamy T, Loughran TP, Jr. How I treat LGL leukemia. Blood. 2011;117:2764-2774.

[29] Chang ST, Hsieh YC, Chen CH, Tsao CJ, Chuang SS. T-cell large granular lymphocytic leukemia with pleomorphic nuclei and colonic infiltration with chronic diarrhea. Leuk Lymphoma. 2010;51:2132-2134.

[30] Kwong YL, Au WY, Leung AY, Tse EW. T-cell large granular lymphocyte leukemia: an Asian perspective. Ann Hematol. 2010;89:331-339.

[31] Gentile TC, Hadlock KG, Uner AH, Delal B, Squiers E, Crowley S, et al. Large granular lymphocyte leukaemia occurring after renal transplantation. Br J Haematol. 1998;101:507-512.

[32] Au WY, Lam CC, Lie AK, Pang A, Kwong YL. T-cell large granular lymphocyte leukemia of donor origin after allogeneic bone marrow transplantation. Am J Clin Pathol. 2003;120:626-630.

[33] Lau LG, Tan LK, Salto-Tellez M, Koay ES, Liu TC. T-cell post-transplant lymphoproliferative disorder after hematopoietic stem cell transplantation: another case and a review of the literature. Bone Marrow Transplant. 2004;34:821-822.

[34] Narumi H, Kojima K, Matsuo Y, Shikata H, Sekiya K, Niiya T, et al. T-cell large granular lymphocytic leukemia occurring after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2004;33:99-101.

[35] Chang H, Kamel-Reid S, Hussain N, Lipton J, Messner HA. T-cell large granular lymphocytic leukemia of donor origin occurring after allogeneic bone marrow transplantation for B-cell lymphoproliferative disorders. Am J Clin Pathol. 2005;123:196-199.

[36] Sabnani I, Zucker MJ, Tsang P, Palekar S. Clonal T-large granular lymphocyte proliferation in solid organ transplant recipients. Transplant Proc. 2006;38:3437-3440.

[37] Kusumoto S, Mori S, Nosaka K, Morita-Hoshi Y, Onishi Y, Kim SW, et al. T-cell large granular lymphocyte leukemia of donor origin after cord blood transplantation. Clin Lymphoma Myeloma. 2007;7:475-479.

[38] Nann-Rutti S, Tzankov A, Cantoni N, Morita-Hoshi Y, Onishi Y, Kim SW, et al. Large Granular Lymphocyte Expansion after Allogeneic Hematopoietic Stem Cell Transplant is Associated with a Cytomegalovirus Reactivation and Shows an Indolent Outcome. Biol Blood Marrow Transplant. 2012;18:1765-1770 [Epub ahead of print].

[39] Gill H, Ip AH, Leung R, So JC, Pang AW, Tse E, et al. Indolent T-cell large granular lymphocyte leukaemia after haematopoietic SCT: a clinicopathologic and molecular analysis. 2012;47:952-956.

[40] Chan JKC, Jaffe ES, Ralfkiaer E, Ko Y-H. Aggressive NK/T-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., ed. WHO classification of tumours of haemtopoietic and lymphoid tissues. Lyon: IARC; 2008:276-277.

[41] Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. Leukemia. 2005;19:2186-2194.

[42] Cheuk W, Chan J, K.C. Chapter 28. NK-cell neoplasms. In: Jaffe ES, Harris NL, Vardiman JW, Campo E, Arber DA, ed. Hematopathology. St. Louis: Saunders; 2011:473-491.

[43] Kim SH, Ko WT, Suh MK, Ha GY, Kim JR. A case of aggressive NK/T-cell lymphoma/leukemia with cutaneous involvement in adolescence. Ann Dermatol (Seoul). 2008;20:77-81.

[44] Chan JKC, Quintanilla-Martinez L, Ferry JA, Peh S-C. Extranodal NK/T-cell lymphoma, nasal type. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., ed. WHO classification of tumours of haemtopoietic and lymphoid tissues. Lyon: IARC; 2008:285-288.

[45] Suzuki R, Suzumiya J, Nakamura S, Aoki S, Notoya A, Ozaki S, et al. Aggressive natural killer-cell leukemia revisited: large granular lymphocyte leukemia of cytotoxic NK cells. Leukemia. 2004;18:763-770.

[46] Yoo EH, Kim HJ, Lee ST, Kim WS, Kim SH. Frequent CD7 antigen loss in aggressive natural killer-cell leukemia: a useful diagnostic marker. Korean J Lab Med. 2009;29:491-496.

[47] Chou WC, Chiang IP, Tang JL, Su IJ, Huang SY, Chen YC, et al. Clonal disease of natural killer large granular lymphocytes in Taiwan. Br J Haematol. 1998;103:1124-1128.

[48] Lee PS, Hwang WS. Aggressive natural killer cell lymphoma/leukemia. Chi Med J (Taipei). 2002;65:622-626.

[49] Ko YH, Park S, Kim K, Kim SJ, Kim WS. Aggressive natural killer cell leukemia: is Epstein-Barr virus negativity an indicator of a favorable prognosis? Acta Haematol. 2008;120:199-206.

[50] Ralfkiaer E, Willemze R, Whittaker SJ. Sézary syndrome. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., ed. WHO classification of tumours of haemtopoietic and lymphoid tissues. Lyon: IARC; 2008:299.