Literature Review:

Hepatosplenic T-cell Lymphoma

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Abstract: *Hepatosplenic T-cell lymphoma (HSTCL) is a rare type of T-cell lymphoma with poor clinical outcomes. Typical clinical features include a predominance of young male with fever, hepatosplenomegaly and cytopenia with the absence of appreciable lymphadenopathy. Diagnosis is based on examination of peripheral blood and histopathology of bone marrow, spleen or liver. In addition, immunophenotyping and cytogenetics are extremely helpful for establishing the diagnosis. Although there is a wide variety of chemotherapy regimen reported for the treatment of HSTCL patients, satisfactory response was rarely obtained. One of the promising results was achieved by the administration of high intensity cytarabine-platinum containing regimen followed by high-dose therapy (HDT) and stem cell transplantation. The role of post-remission therapy with allogeneic stem cell transplantation, a potentially curative therapy, is not clearly demonstrated. With paucity of evidence, no satisfactory recommendation could be made.*

Key Words : ● *Hepatosplenic T-cell lymphoma* ● *Diagnosis* ● *Treatment*

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Introduction

Hepatosplenic T-cell lymphoma (HSTCL) is a rare type of lymphoma, accounting for 1.4% of T-cell lymphomas (TCL).[1] Most cases express the $\delta\gamma$ T-cell receptor (TCR) while the minority of cases express the $\alpha\beta$ TCR, still both types of T-cell origin are included under the term HSTCL by the 2008 WHO classification of lymphomas.[2] HSTCL is more common in young men presenting with B-symptoms, hepatosplenomegaly, cytopenia without significant lymphadenopathy along with the poor outcomes.[3]

Historical background

HSTCL was first described by Farcet et al. in 1990 as a distinct lymphoma entity in two patients, presenting with predominately hepatosplenomegaly.[4] Six years later, Cooke et al. reported 7 cases of HSTCL. Nearly all were young adult males and had typical presentation including marked hepatosplenomegaly, thrombocytopenia, without lymphadenopathy or significant lymphocytosis. TCR-γ gene rearrangement was detected in all cases.[5] Currently, more than 200 cases were reported including 20 cases in Asia[6] which might be underestimated as the clinical feature is not typical for lymphoma as well as the difficulty in demonstration of the $\delta\gamma$ T-cell origin.[7,8]

Epidemiology

In Thailand, analysis of 1,983 cases of lymphoma in Siriraj Hospital from 1993 to 2002 revealed only 3 HSTCL cases or frequency less than 1%[9] and none from 939 lymphoma patients was reported by the Thai Lymphoma Study Group during 2007 and 2009.[10]

The HSTCL typically occurs in young male at the age of 30 to 40 years.[11,12] Immunosuppression is the

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most important risk factor, especially post solid-organ transplantation including kidney,[13-16] heart,[17] and liver transplantation.[18] There are growing evidences that HSTCL is associated with a treatment of inflammatory bowel disease (IBD) with tumor necrosis factor-alpha (TNF-α) inhibitors (infliximab and adalimumab)[19-21] and immunomodulators especially thiopurines (azathioprine or 6-mercaptopurine [6-MP]).[22-25]

Pathogenesis[7,8]

Most of HSTCL is believed to derive from the subset of immature or nonactivated cytotoxic $\delta\gamma$ T cells of the splenic pool with Vδ1 gene usage. Uncommon $\alpha\beta$ TCR phenotype seems to be a variant form of $\delta\gamma$ HSTCL. Pathogenesis of the disease may be related to chronic antigenic stimulation in the immunocompromised setting. These patients might have defect in the clearance of pathogen, which results in excessive antigen stimulation of T-cells, especially $\delta\gamma$ T-cells that have limited antigen-specific TCRs. This might be the initial event of malignant clonal expansion. Additional transforming events, for example isochromosome 7q (i[7q]), consequently develop, then these neoplastic clones spread to intrasinusoidal part of liver, spleen and bone marrow, making clinical features of HSTCL.

Clinical presentation

Most patients present with hepatosplenomegaly, B-symptoms and peripheral blood cytopenia. Lymphadenopathy is usually minimal or absent as shown in table 1.[6,11,12,26,27] Blood chemistry usually shows abnormal liver function tests (LFTs) and lactate dehydrogenase (LDH) elevation. Although the majorities of patients have bone marrow involvement, it may be subtle and cannot be recognized easily on bone marrow biopsy. Other uncommon manifestation includes hemophagocytic syndrome[12,28], autoimmune hemolytic anemia[29-32] and immune thrombocytopenia.[33]

Diagnosis

Complete blood count (CBC) and peripheral blood smear (PBS)

As shown in Table 1, cytopenia is common in all series. Atypical lymphoid cells were detected in peripheral blood in many case reports; however, absolute lymphocyte count was not elevated.[12,26]

Bone marrow aspiration and biopsy

In the majority of reported cases, the diagnosis of HSTCL was based on pathology from spleen after splenectomy and/or liver biopsy. Bone marrow aspiration specimens usually show hypercellular with trilineage hyperplasia, accompanied with moderate infiltration (15-30%) of abnormal lymphoid cells. They have intrasinusoidal pattern of infiltration. However, interstitial infiltration is frequently observed when disease progression. As lymphoma cells in BM are discrete and difficult to detect, the immunohistochemistry of bone marrow biopsy specimens is required to the demonstration of abnormal cells.[7] Additional diagnostic clues are hyperplasia of the non-involved marrow with or without dysplastic features and hemophagocytosis.[34]

Flow cytometry

Flow cytometry of the peripheral blood or bone marrow are important and can help with an earlier diagnosis. There is the uniform flow cytometric immunophenotype of circulating T-cells with CD2+, CD3+, down-regulation of CD5 and/or CD7, double negative for CD4 and CD8 and commonly positive for NK cell markers (CD16+ and CD56+).[35]

Pathology[2,8]

Tissue histopathology is required for diagnosis of HSTCL. Cytology is unsuitable for diagnosis because of wide variation of cytological features from mature to blast-like lymphoid cells. Some patients required splenectomy for tissue diagnosis.[12] Image-guided core-needle biopsy of liver, leading to 41.2% of diagnosis in Chinese case series[6], is also useful for diagnosis. According to pathologic findings, the spleen is usually massively enlarged without focal lesion. Tumor cells

Table 1 Clinical manifestation of HSTCL in selected case series

	Weidmann E, et al.*[11]	Belhadj K, et al.[12]	Falchook GS, et al.[26]	Wei SZ, et al.[27]	Lu CL, et al.[6]
Number of patients	45	21	15	8	17
Median age (range)	29 (5-68)	34 (16-58)	38 (21-64)	29 (12-52)	23 (11-51)
Male : female ratio	75 : 25	77 : 33	60 : 40	75 : 25	71 : 29
History of immunocompromise (%)	7	19	27	0	0
Sites of involvement (%)					
Splenomegaly					
Hepatomegaly					
Abnormal LFTs Lymphadenopathy	97.5	100	100	100	100
Bone marrow	80	77	40**	100	88.2
Peripheral blood involvement	43	38	40	100	100
	6.7	0	13	13	11.8
	72	100	100	28	53.3
	50	48	27	NA	NA
B symptoms	70	67			76.5
Fever	NA	NA	67	100	NA
Night sweats	NA	NA	60	NA	NA
Weight loss	NA	NA	53	75	NA
Cytopenias					
Anemia	84	77	73	85	88.2
Thrombocytopenia Neutropenia	85	95	64	71	58.8
	45	58	36	NA	76.5
Elevation of LDH	62	55	NA	71	69

NA = not available; *Data from previous case reports until year 2000

**Although 40% of patients had hepatomegaly but 67% had liver involvement

diffusely infiltrate the red pulp which leads to marked reduction or complete loss of the white pulp. Liver also has diffuse enlargement with marked expansion of the sinusoids with sparing of the portal triads and hepatocytes. The neoplastic cells are usually monomorphic small to medium-sized having round or indented nuclei with dispersed chromatin and inconspicuous nucleoli. They usually have pale and abundant cytoplasm, most without azurophilic granules, and rare mitotic figures.

Immunophenotype and genotype[8]

The neoplastic cells have the phenotype and genotype of immature cytotoxic T cells with CD3+, CD2+, CD5-, CD7+/- with either TCR-$\delta\gamma$+ or TCR-$\alpha\beta$+. In cases of $\delta\gamma$ subtype are CD4-/CD8- or more rarely CD4-/CD8+. An aberrant T-cell phenotype such as the loss of CD3, CD5 and/or CD7 is frequently found. NK-related antigens CD16 and CD56, except CD57, are commonly positive. Almost all cases have an inactive cytotoxic phenotype, as shown by the presence of granular cytoplasmic TIA1 staining but do not express granzyme B and perforin. Cases of $\alpha\beta$ HSTCL have the same clinicopathologic features.

In molecular study, the majority of cases show a clonal TCR-γ gene rearrangement, as demonstrated by polymerase chain reaction (PCR) studies. Southern blot analyses of TCRβ and δ chain genes show the clonality and Vδ1 rearrangements are the predominant molecular patterns. Classification of $\delta\gamma$ TCL and $\alpha\beta$ TCL can be done accurately by using TCR-associated gene signature.

Cytogenetic study

Isochromosome 7q [i(7q), mostly i(7)(q10)] are reported in most cases which frequently occur in association with trisomy 8 or loss of a sex chromosome.[36-40] In one study, i(7q) was associated with predominance of 7q signals and correlated with cytologic features of

progression.[38] These findings support that i(7q) is the primary cytogenetic abnormality in HSTCL, and plays an important role in the pathogenesis and evolution of this disease.[40]

Treatment

There are many treatment options for HSTCL including conventional chemotherapy, purine analogues, interferon-alpha, autologous (ASCT) and allogeneic hematopoietic stem cell transplantation. In the setting of posttransplantation related HSTCL, theRreduction of immunosuppression alone is not effective and chemotherapy should be gives.[4]

Conventional chemotherapy

HSTCL has poor and non-durable response to conventional chemotherapt. In report from Belhadj K, et al., most patients transiently responded to CHOP-like regimen (overall response rate; OR 63%) or platinum-cytarabine-based regimen OR 100%), but relapsed shortlyi[12] two patients who alive more than 40 months received platinum-cytarabine–based regimen followed by ASCT. Salvage regimen such as an ESHAP (etoposide, methylprednisolone, cytarabine, cisplatie) and hyperCVAD (cyclophosphamide, vincristine, adriamycie, dexamethasone, high dose methotrexate, high dose cytarabine) regimen can be used in patients, Rnot achieving CR after front-line therapy. There was a case report of HSTCL in renal allograft recipient who had a durable remission more than 8 yeard by given hyperCVAD regimendin combination with greduction of immunosuppressive therapy.[4]

Nucleoside analogue

Successful treatment of relapsed[43-45] and newly diagnosed HSTCL[46] before undergoing ASCT by 2'-deoxycoformycin (pentostatin) have been reported. Another nucleoside analogue, cladribine, in combination with alemtuzumab, resulted in a prolonged clinical and molecular remission over 2 years in one case report.[47] According to safety profile, 2 patients who, received pentostatin suffered from acute respiratory distress syndrome and invasive fungal infectios.[48] As a result, optimal strategies to balance between efficacy and adverse side effect of these drugs in HSTCL are needed.

Interferon-alpha (IFN-α)

IFN-α monotherapy could induce durable remission in two HSTCL patients with and without Crohn's diseasy.[49] In this report, IFN-α was started at 1 million units (MU) subcutaneous daily and titrated up to 5.1 and 6 MU daily then continued for 12 and 9 months, respectively. Both patients were in clinical remission more than 20 months.

Novel therapy

Proteosome inhibitors, bortezomib, in combination with high-dose CHOP-like chemotherapy (ACVB; adriamycin, cyclophosphamide, vincristine, bleomycin, and prednisone) followed by ASCT is one of effective salvage therapy for HSTCL with a durable remission over 2 years in a patien, achieving only PR after platinum-cytarabine-based chemotherapy.[50]

Autologous stem cell transplantation (ASCT)

Durable remission after ASCT has been reported in many case seriess.[12,51,52] From Stanford study, two patients with HSTCL who underwent ASCT in first remission after CHOP chemotherapy have been in complete remission more than 5 years.[51]

Allogeneic stem cell transplantation (Allogeneic-SCT)

Allogeneic SCT can induce durable remission in patients in first or subsequent remissionnor having refractory disease. From French study of allogeneic-SCT for various types of aggressive T-cell lymphomas, 2 of 3 cases of HSTCL had durable complete remissiondwhile one case died from pulmonary infection.[53] From a review of literature, 7 of 17 (41%) patients with $\delta\gamma$ HSTCLshad durable remission after underwent allogeneic-SCT.[5R] Lacking evidences to give a general recommendation, the consolidation with allogeneic-SCT is a potentially curable treatment and should beooffered to all transplant candidate patients.[55]

In conclusion, there are a wide variety of chemotherapy regimens with limited efficacy for HSTCL. Despite their efficacy in term of satisfactory response to induction, no

clinical benefits could have been demonstrated in long term. High intensity cytarabine-platinum containing regimen followed by high-dose therapy (HDT) and stem cell transplantation has been shown to achieve promising results. The exact role of post-remission therapy with allogeneic stem cell transplantation, a potentially curative therapy, could not be clearly demonstrated. With paucity of evidence, the recommendations could not be made with satisfaction.

Prognosis

HSTCL is a very aggressive lymphoma showing a poor prognosis with a median overall survival less than 2 years and poor response to standard chemotherapy. From International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, 5-year overall survival was only 7% in and 5-year failure-free survival was 0% which was the worst among all subtypes of T-cell lymphomas.[1] The international prognosis index (IPI) score is not a good risk stratification method since patients with low IPI also had poor outcomes.[1] Factors predicting poorer outcomes wers male gender, liver involvement, and history of immunocompromise.[2]

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บทความฟื้นวิชา

Hepatosplenic T-cell Lymphoma

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บทคัดย่อ *Hepatosplenic T-cell lymphoma (HSTCL) เป็นมะเร็งต่อมน้ำเหลืองชนิดทีเซลล์ซึ่งพบได้น้อยมากและมีผลการรักษาที่ไม่ดี ลักษณะทางคลินิกเฉพาะเป็นผู้ชายอายุน้อยมาด้วยไข้ ตับม้ามโต และมีเม็ดเลือดต่ำโดยไม่มีต่อมน้ำเหลืองโตชัดเจน การวินิจฉัยสามารถทำได้โดยการตรวจสเมียร์เลือดและการตรวจทางพยาธิวิทยาจากไขกระดูก ม้ามหรือตับ นอกจากนี้การตรวจ immuonophenotyping และcytogenetics สามารถช่วยในการวินิจฉัยได้มาก มีการศึกษาเกี่ยวกับการรักษาด้วยยาเคมีบำบัดหลายสูตรแต่ได้ผลที่ได้ยังไม่เป็นที่น่าพอใจ โดยยาเคมีบำบัดซึ่งมี cytarabine ขนาดสูงร่วมกับ platinum ต่อด้วย high-dose therapy และการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดมีแนวโน้มว่าจะได้ผลดี ส่วนบทบาทของการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดชนิด allogeneic ซึ่งมีโอกาสทำให้โรคหายขาดได้นั้นยังไม่ชัดเจน เนื่องจากหลักฐานการศึกษาไม่มากนักทำให้ยังไม่มีคำแนะนำที่เหมาะสมสำหรับการรักษาผู้ป่วยกลุ่มนี้*

Key Words : ● *Hepatosplenic T-cell lymphoma* ● *Diagnosis* ● *Treatment*
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