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

Historical background
HSTCL was first described by Farcet et al. in 1990 as a distinct lymphoma entity in two patients, presenting with predominately hepatosplenomegaly. 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. Currently, more than 200 cases were reported including 20 cases in Asia which might be underestimated as the clinical feature is not typical for lymphoma as well as the difficulty in demonstration of the δγ T-cell origin.

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% and none from 939 lymphoma patients was reported by the Thai Lymphoma Study Group during 2007 and 2009.

The HSTCL typically occurs in young male at the age of 30 to 40 years. Immunosuppression is the
most important risk factor, especially post solid-organ transplantation including kidney, heart, and liver transplantation. 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) and immunomodulators especially thiopurines (azathioprine or 6-mercaptopurine [6-MP]).

Pathogenesis

Most of HSTCL is believed to derive from the subset of immature or nonactivated cytotoxic δγ T cells of the splenic pool with Vδ1 gene usage. Uncommon αβ TCR phenotype seems to be a variant form of δγ 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 δγ 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. 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, autoimmune hemolytic anemia and immune thrombocytopenia.

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.

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. Additional diagnostic clues are hyperplasia of the non-involved marrow with or without dysplastic features and hemophagocytosis.

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+).

Pathology

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. Image-guided core-needle biopsy of liver, leading to 41.2% of diagnosis in Chinese case series, is also useful for diagnosis. According to pathologic findings, the spleen is usually massively enlarged without focal lesion. Tumor cells
Hepatosplenic T-cell Lymphoma

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**

The neoplastic cells have the phenotype and genotype of immature cytotoxic T cells with CD3+, CD2+, CD5-, CD7+/+ with either TCR-δγ+ or TCR-αβ+. In cases of δγ 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 αβ 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 δγ TCL and αβ TCL can be done accurately by using TCR-associated gene signature.

**Cytogenetic study**

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

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### Table 1 Clinical manifestation of HSTCL in selected case series

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<tbody>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>21</td>
<td>15</td>
<td>8</td>
<td>17</td>
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<tr>
<td>Median age (range)</td>
<td>29 (5-68)</td>
<td>34 (16-58)</td>
<td>38 (21-64)</td>
<td>29 (12-52)</td>
<td>23 (11-51)</td>
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<tr>
<td>Male : female ratio</td>
<td>75 : 25</td>
<td>77 : 33</td>
<td>60 : 40</td>
<td>75 : 25</td>
<td>71 : 29</td>
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<td>History of immunocompromise (%)</td>
<td>7</td>
<td>19</td>
<td>27</td>
<td>0</td>
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**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
  - Peripheral blood involvement: 6,7 0 13 13 11,8
  - Peripheral blood involvement: 72 100 100 28 53,3
  - Peripheral blood involvement: 50 48 27 NA NA

**B symptoms**

- 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 51,8
- Thrombocytopenia Neutropenia: 45 58 36 NA 71,6
- Thrombocytopenia Neutropenia: 62 56 NA 71 69

**Elevation of LDH**

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

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

**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, the reduction of immunosuppression alone is not effective and chemotherapy should be given.  

**Conventional chemotherapy**

HSTCL has poor and non-durable response to conventional chemotherapy. 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 shortly 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, cisplatin) and hyperCVAD (cyclophosphamide, vincristine, adriamycine, dexamethasone, high dose methotrexate, high dose cytarabine) regimen can be used in patients, but not 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 year by given hyperCVAD regimen in combination with greduction of immunosuppressive therapy.

**Nucleoside analogue**

Successful treatment of relapsed and newly diagnosed HSTCL 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. According to safety profile, 2 patients who, received pentostatin suffered from acute respiratory distress syndrome and invasive fungal infections. 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 disease. 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 patient, achieving only PR after platinum-cytarabine-based chemotherapy.

**Autologous stem cell transplantation (ASCT)**

Durable remission after ASCT has been reported in many case series. 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.

**Allogeneic stem cell transplantation (Allogeneic-SCT)**

Allogeneic SCT can induce durable remission in patients in first or subsequent remission or 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 remission while one case died from pulmonary infection. From a review of literature, 7 of 17 (41%) patients with δγ HSTCL had durable remission after underwent allogeneic-SCT. Lacking evidences to give a general recommendation, the consolidation with allogeneic-SCT is a potentially curable treatment and should be offered to all transplant candidate patients.

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. The international prognosis index (IPI) score is not a good risk stratification method since patients with low IPI also had poor outcomes. Factors predicting poorer outcomes were male gender, liver involvement, and history of immunocompromise.

References

Hybridization study of chromosome 7 aberrations in hepatosplenic T gamma/delta lymphoma.


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บทความพื้นฐาน

Hepatosplenic T-cell Lymphoma

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บทคัดย่อ Hepatosplenic T-cell lymphoma (HSTCL) เป็นมะเร็งต่อมน้ำตาลชนิดที่เป็นที่พบได้น้อยมากและมีผลการรักษาที่ไม่ดี ลักษณะทางคลินิกเฉพาะเป็นผู้ชายอายุน้อยมากมีไข้ ตับม้ามToEnd และมีเม็ดเลือดต่ำโดยไม่มีต่อมน้ำตาลชัดเจน การวินิจฉัยสามารถทำได้โดยการตรวจเลือดและการตรวจทางพยาธิวิทยาจากไขกระดูก ร่ำพื้นดี และจากการตรวจ immuno phenotyping และcytogenetics สามารถช่วยในการวินิจฉัยได้มาก มีการศึกษาเกี่ยวกับการรักษาด้วยยาเคมีบำบัดหลายสูตรแต่ได้ผลที่ไม่เป็นที่น่าพอใจ โดยยาเคมีบำบัดที่มี cytarabine ขณะอยู่ร่วมกับ platinum ต้องมี high-dose therapy และการปลูกถ่ายเซลล์ต้นกำเนิด เม็ดเลือด มีแนวโน้มว่าจะได้ผลดี ส่วนบทบาทของการปลูกถ่ายเซลล์ต้นกำเนิดโดย เลือดชุด allogeneic ซึ่งมีโอกาสทำให้โรคหายขาดได้นั้นยังไม่ชัดเจน เนื่องจากหลักฐานการศึกษาไม่มากนักทำให้ไม่ได้ผลเท่าที่เหมาะสมสำหรับการรักษาผู้ป่วยกลุ่มนี้

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

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