中文題目：台灣皮下脂層炎樣 T 細胞淋巴瘤病人的 *HAVCR2* 基因生殖系變異

英文題目：*HAVCR2* Germline Mutations in Taiwanese Subcutaneous Panniculitis-Like T-cell Lymphoma Patients

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Background:

Subcutaneous panniculitis-like T-cell lymphoma (SPTL) is a very rare subtype of peripheral T-cell lymphomas which infiltrates the subcutaneous tissue. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening complication in SPTL patients. SPTL patients with HLH had significantly worse overall survival compared with those without HLH (5-year OS 46% vs. 91%). Recent studies have demonstrated that germline hepatitis A virus-cellular receptor 2 (*HAVCR2)* mutations were identified in up to 51-85% of SPTL patients, and were associated with a higher risk of HLH. *HAVCR2* encodes t-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), which is a member of the TIM family and is expressed by several cell types of the immune system. However, data from the Chinese or Taiwanese population is lacking, and there is only one small-sized cohort with 13 Asian patients reported to date. Our previous work has demonstrated a high incidence of HLH and a rather aggressive clinical course in Taiwanese SPTL patients. Therefore, we hypothesized that Asian SPTL patients may have different genetic backgrounds and biological characteristics, which leads to a more malignant phenotype and higher risk of HLH. The aim of this study is to analyze the clinical features and germline *HAVCR* genotype of Taiwanese SPTL patients.

Method:

Patients diagnosed with SPTL at Taipei Veterans General Hospital between June 1994 and April 2020 were retrospectively reviewed. Additional Beta F1 staining was performed to confirm α/β phenotype if not previously done. Clinical data collected included: sex, date of diagnosis, age at diagnosis, the extent of skin lesions, location of skin lesions, presence of HLH, bone marrow involvement, extracutaneous involvement, and staging at diagnosis. HLH was defined according to the HLH-2004 criteria. TNM classification proposed by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) was adopted for staging. Histological descriptions, immunohistochemical findings, and PCR analysis of T-cell receptor (TCR) gene rearrangement were recorded and evaluated. Germline DNA from formalin-fixed paraffin-embedded (FFPE) skin biopsy samples was extracted using the QIAamp DNA-FFPE tissue kit. *HAVCR2* genotypes were analyzed by Sanger sequencing and ABI

3730XL DNA Analyzer.

Result:

Thirteen SPTL patients were included in the study. The median patient age was 24 years (range 11–40 years). Most patients (n = 12) were presented with skin nodules or plaques. Nine patients had T3 disease at diagnosis. The frequency of HLH was strikingly high in this cohort (53.8%). Germline DNA was available in 5 patients. *HAVCR2* p.Y82C (c.245A> G) mutations were identified in all 5 patients. Four patients harbored heterozygous Y82C mutations, while homozygous Y82C mutations were discovered in only one patient. None of the patients harbored *HAVCR2* p.I97M mutation or compound mutations. Among these *HAVCR2*^{Y82C} mutated patients, 2 developed HLH (40%). It is worth noting that the patient with homozygous Y82C mutation died of highly aggressive HLH.

Conclusions:

Homozygous and heterozygous *HAVCR2*^{Y82C} mutations were identified in Taiwanese SPTL patients. SPTL was associated with homozygous *HAVCR2*^{Y82C} mutations in previous reports. Our findings suggest that heterozygous *HAVCR2*^{Y82C} mutations may also be a cancer-predisposing genetic alteration.