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# HAVCR2 mutations are associated with severe hemophagocytic syndrome in subcutaneous panniculitis-like T-cell lymphoma: a study by the GFELC

**Short title:** HAVCR2 mutations and long-term SPTCL outcome

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Subcutaneous panniculitis-like T cell lymphoma (SPTCL) is a rare cutaneous T-cell lymphoma characterized by a hypodermal infiltration of CD8 T-cells expressing an  $\alpha\beta$  T-cell receptor (TCR).

Since 2005, SPTCL is considered as a distinct entity from  $\gamma\delta$  T-cell lymphoma in the World Health Organization (WHO)/European Organization for Research and Treatment of Cancer (EORTC) classification (1).

An EORTC study of 63 cases showed the excellent prognosis of SPTCL without associated hemophagocytic syndrome (HPS) and questioned the use of polychemotherapy as first-line treatment (2).

These results were supported by 2 recent studies (2,3).

However, a minority of patients develop aggressive disease, the determinants of which are not understood. The presence of HPS is associated with shorter overall survival (4).

A recent study has identified germline homozygous or compound heterozygous loss-of-function Hepatitis A Virus Cellular Receptor 2 (HAVCR2, encoding T-Cell Immunoglobulin And Mucin Domain-Containing Protein 3 (TIM-3)) mutations, in 59% of familial SPTCL (5). The mutation was found at a high prevalence (85%) in sporadic Asian cases (6). The prevalence of the HAVCR2 mutation and long-term clinical outcome have not yet been studied in a large European SPTCL cohort.

We studied the clinical presentation, long-term evolution and the occurrence of HAVCR2 mutation in a cohort of 70 patients with sporadic SPTCL.

We performed a retrospective multicenter study of 70 sporadic SPTCL cases from 19 French centers, diagnosed between 2000 and 2019.

The cases were identified using the national French Cutaneous Lymphoma group (GFELC) or local databases. All samples were collected with informed consent following approval of the institutional review boards of the respective institutions. All cases were reviewed by the expert physicians and pathologists from the GFELC during national multidisciplinary meetings. The diagnosis of  $\gamma\delta$  T-cell lymphoma was excluded by the presence of a clonal rearrangement of the TCR $\beta$  and/or histological and immunohistochemical features (CD8+CD56-CD30-granzyme B+TiA1+ $\beta$ F1+TCR $\delta$ -). HPS was defined according to the HLH 2004 criteria (7). HPS was considered severe if patients required intensive care and/or had severe cytopenias (Hemoglobin<6g/dL; Platelets<50G/L; Neutrophils<0.5G/L).

Twenty-seven cases have been previously reported (2), follow-up was updated.

DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor tissue (n=39), peripheral blood (n=11) or both (n=3), using the QIAamp DNA-FFPE tissue kit or Blood Mini Kit respectively (Qiagen). Primers flanking exon 2 of the HAVCR2 gene were used to screen the HAVCR2 mutation in 53 cases with available material. The purified PCR products were bidirectionally sequenced on an ABI 3730XL DNA Analyzer (Applied Biosystems). Primers and PCR conditions are available upon request. TIM-3 expression was studied by immunohistochemistry (anti-human TIM-3 antibody, CST 45208, Cell signal).

Out of 70 patients, 55 were women. Median age was 42 (range, 1–90 years). Twenty-five patients (38%) had a history of autoimmune disease (13 lupus erythematosus). Thirteen patients had a previous history of panniculitis (9 lupus panniculitis). Eleven cases displayed histological similarities with lupus erythematosus. Autoantibodies were frequently detected (62%) especially antinuclear antibodies, even in patients without autoimmune disease history. HPS was found in 12 patients (18%) including 5 severe forms. The main clinical and biological characteristics are described in **Table 1** and detailed in **Table S1**.

The median follow-up was 35 months (range, 5 days-22 years). Out of 67 patients with follow-up data, 49 (73%) were in complete response (CR), 5 in partial response (PR), 8 had progressive disease (PD). Five patients died, one from disease progression and HPS, 3 in CR, 1 in PR. The median duration of CR was 29.7 months (0-22years). Twenty-one patients relapsed during the follow-up (32%).

Most patients (76%) received immunomodulatory drugs as first-line treatment (corticosteroids and/or low-dose methotrexate in most cases, ciclosporin, hydroxychloroquine, chloraminophene,  $\alpha$ -interferon, alone or in combination).

Seventeen patients received polychemotherapy (25%), 11 as first-line treatment (16%). The CR rate was not significantly different between patients who received immunomodulatory drugs or chemotherapy as first-line treatment.

Patients with severe HPS underwent autologous (3/5) or allogeneic (1/5) hematopoietic stem-cell transplant (HSCT) or etoposide-based chemotherapy (5/5), 2 of them after failure of immunomodulatory treatment. Treatments are detailed in **Table 1**.

Out of 53 patients with available suitable material for Sanger sequencing, a biallelic HAVCR2 mutation was detected in 13 cases (25%). Half of the mutated cases originated from East Asia or Polynesia, 1 from the Reunion Island and 2 from North Africa. All the patients with Asian or Polynesian ancestry harbored the homozygous p.Tyr82Cys HAVCR2 variant,

whereas the 3 with European ancestry, one from North Africa and the patient from the Reunion Island harbored the homozygous p.Ile97Met variant. The second patient from North Africa was compound heterozygous (p[Tyr82Cys]+[Ile97Met]) (**Table S2**).

Most of the clinical, pathological and biological findings did not differ between the mutated and wild-type groups (**Table 2**).

However, in mutated cases, HPS was more frequent (4/13 versus 5/40) and significantly more severe (3/13 versus 0/40,  $p=0.02$ ) and polychemotherapy was significantly more often used (8/12 versus 5/39,  $p=0.01$ ), especially to achieve CR (5/10 versus 3/31;  $p=0.04$ ); for 3 of them, polychemotherapy was used after failure of immunomodulatory treatment. The use of HSCT was significantly more frequent in mutated cases (4/13 versus 1/40;  $p=0.02$ ). Severe HPS was found in both patients with the p.Ile97Met variant ( $n=1$ ) and with the p.Tyr82Cys variant ( $n=2$ ).

The relapse and CR rate were not significantly different between mutated and wild-type cases. In mutated cases, TIM-3 immunohistochemistry staining was cytoplasmic, paranuclear, without membrane staining, whereas it was cytoplasmic and membranous in wild-type cases (**Figure S1**).

This retrospective study of 70 SPTCL cases is, to our knowledge, the largest reported series of this rare disease so far, and the first to evaluate the frequency of sporadic HAVCR2 mutations in the European population and its relation to severe HPS.

One patient died of SPTCL, and this better prognosis as compared to the EORTC study could be linked to the growing use of immunomodulatory drugs as first-line treatment (2,3).

Eighty-one percent of patients achieved CR, with no significant difference between patients treated with immunomodulatory drugs versus polychemotherapy.

The prevalence of HAVCR2 mutations in our study was significantly lower than in the recently published Asian SPTCL study (6) (25% versus 85%), consistent with the higher

prevalence of the p.Tyr82Cys minor allele frequency in East Asians (0.02 versus 0.003) (5). All mutated Asian patients harbored the p.Tyr82Cys variant; by contrast, six of our patients harbored the p.Ile97Met variant. Out of 13 previously reported Asian patients (6), 4 (31%) presented with HPS. Interestingly, in our study, severe HPS was only observed in patients harboring an HAVCR2 mutation. The rare patients with an HAVCR2 mutation and severe HPS required intensive treatment with chemotherapy +/- HSCT. This is consistent with previously published articles on Asian patients (8,9) showing that a subgroup of patients present with aggressive disease that does not respond to corticosteroids in half of the cases (8) and may require HSCT (9). The early diagnosis of an HAVCR2 mutation in European cases could help identify the few patients with an aggressive evolution, requiring intensive treatment. Our results suggest that SPTCL overall is characterized by a good prognosis, and can be treated with immunomodulatory drugs as first-line treatment, supporting the concept of an inflammatory condition with T-cell lymphoproliferation. However, some cases have a severe presentation and require aggressive treatments. These cases are significantly associated with HAVCR2 mutations.



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## Tables

**Table 1.** Main clinical, biological characteristics, and treatments in 70 patients with subcutaneous panniculitis-like T-cell lymphoma in the study cohort

<b>Patients</b>	<b>n = 70 (%)</b>
<b>History of autoimmune disease</b>	<b>25/68 (37)</b>
Lupus erythematosus	13/68(19)
Rheumatoid arthritis	4/68 (6)
Antiphospholipids syndrome	4/68 (6)
Overlap syndrome	2/68 (3)
Autimmune cytopenia	2/68 (3)
Basedow thyroiditis	2/68 (3)
Autoimmune cytopenia	2/68 (3)
Multiple sclerosis	1/68 (2)
Alopecia areata	1/68 (2)
<b>Clinical abnormalities</b>	
Lesions size	
1-5cm	16/38 (42)
5-10cm	12/38 (32)
>10cm	9/38 (24)
Morphology of the lesions	
Nodules	53/61 (87)
Plaques	16/61 (26)
Ulceration	6/61 (10)
Number of lesions	
Single	5/68 (7)
Multiple	63/68 (93)
Localisation of the lesions	
Upper limb	36/68 (53)
Lower limb	42/68 (62)
Trunk	37/68 (54)
Head	15/68 (22)

B symptoms	46/67 (69)
Fever	36/67 (54)
Weight loss	19/67 (28)
Asthenia	36/67 (54)
Lymphadenopathy	21/66 (32)
Splenomegaly	11/65 (17)
Hepatomegaly	11/66 (17)
<b>Biological abnormalities</b>	
Haemophagocytic syndrome	12/68 (18)
Auto-antibodies	32/52 (62)
Anti-nuclear antibodies (titer >1/80)	30/52 (58)
<b>Treatments</b>	
Polychemotherapy	17/68 (25)
Polychemotherapy as first-line treatment	11/68 (16)
Followed by an autologous stem cell transplantation	4/68 (6)
Followed by an allogeneic stem cell transplantation	1/68 (2)
Polychemotherapy as second-line treatment	6/68 (9)
Followed by an autologous stem cell transplantation	1/68 (2)
Followed by an allogeneic stem cell transplantation	1/68 (2)
Immunosuppressive drug as first-line treatment	52/68 (76)
Corticosteroids	16/68 (24)
Corticosteroids + low dose methotrexate	12/68 (18)
Hydroxychloroquine	8/68 (12)
Low-dose methotrexate	7/68 (10)
Corticosteroids + hydroxychloroquine	2/68 (3)
Alpha-interferon	2/68 (3)
Chloraminophene	1/68 (2)
Corticosteroids + ciclosporine	1/68 (2)

**Table 2.** Comparison of mutated and wild type HAVCR2 cases

	<b>HAVCR2 mutated, n (%)</b>	<b>HAVCR2 wild-type, n (%)</b>	<b>p value</b>
Number of patients	13	40	
Median age (years)	34 (15-90)	44 (1-71)	ns
Sex (F/M)	10/3	31/9	ns
History of autoimmune disease	3/11 (27)	17/39 (44)	ns
B symptoms	11/12 (92)	24/38 (63)	ns
HPS	4/13 (30)	5/40 (13)	ns
<b>Severe HPS*</b>	<b>3/13 (23)</b>	<b>0/40 (0)</b>	<b>0.02</b>
Auto-antibodies	5/8 (63)	16/31 (52)	ns
<b>Polychemotherapy</b>	<b>8/12 (67)</b>	<b>5/39 (13)</b>	<b>0.01</b>
- To achieve CR	<b>5/10 (50)</b>	<b>3/31 (10)</b>	<b>= 0.04</b>
Immunosuppressors	9/13 (69)	33/40 (83)	ns
- To achieve CR	5/10 (50)	27/31 (87)	ns
<b>Stem cell transplant</b>	<b>4/13 (31)</b>	<b>1/40 (2.5)</b>	<b>0.02</b>
- autologous	3/13 (23)	1/40 (2.5)	ns
- allogeneic	1/13 (8)	0/40 (0)	ns
CR	10/13 (77)	31/40 (78)	ns
Median CR duration (months)	25.5	26.5	ns
Relapse	3/12 (25)	10/37 (27)	ns
Deceased	2/13 (15)	2/39 (5)	ns
- from SPTCL	0/2	1/2	ns

*Abbreviations: SPTCL, subcutaneous panniculitis-like T-cell lymphoma; F, female; M, male; CR, complete remission; ns, not significant*