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TO THE EDITOR:

HAVCR2 mutations are associated with severe hemophagocytic syndrome in subcutaneous panniculitis-like T-cell lymphoma

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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 αβ T-cell receptor. Since 2005, SPTCL has been considered a distinct entity from γδ T-cell lymphoma in the World Health Organization/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 further supported by 2 recent studies.[2,3] However, a minority of patients develops aggressive disease, the determinants of which are not understood. The presence of HPS accompanying SPTCL 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 clinical outcome have not yet been studied in a large European SPTCL cohort.

We studied the clinical presentation, long-term evolution, and 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 or local databases. All samples were collected with informed consent after approval of the institutional review boards of the respective institutions. All cases were reviewed by the expert physicians and pathologists from the French Cutaneous Lymphoma group during national

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

Patients	n = 70 (%)
Ethnicity	
Europe	37/63 (59)
Asia*	9/63 (14)
North Africa	7/63 (11)
Sub-Saharan Africa	4/63 (6)
Caribbean Islands	3/63 (5)
Polynesia	3/63 (5)
History of autoimmune disease	25/68 (37)
Lupus erythematosus	13/68 (19)
Rheumatoid arthritis	4/68 (6)
Antiphospholipids syndrome	4/68 (6)
Overlap syndrome	2/68 (3)
Autoimmune cytopenia	2/68 (3)
Autoimmune thyroiditis	2/68 (3)
Autoimmune cytopenia	2/68 (3)
Multiple sclerosis	1/68 (2)
Alopecia areata	1/68 (2)
Clinical abnormalities	
Lesions size	
1-5 cm	16/38 (42)
5-10 cm	12/38 (32)
>10 cm	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)
Localization 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)
Biological abnormalities	
Hemophagocytic syndrome	12/68 (18)
Auto-antibodies	32/52 (62)
Anti-nuclear antibodies (titer > 1/80)	30/52 (58)
Treatments	
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 (77)
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)
α-interferon	2/68 (3)
Chloraminophene	1/68 (2)
Corticosteroids + cyclosporine	1/68 (2)

*Including: Vietnam (n = 4), Cambodia (n = 2), Bangladesh (n = 1), China (n = 1), not precise (n = 1)

†Including the following regimen: CHOP (cyclophosphamide, adriamycin, vincristine, prednisone); CHOEP (CHOP + etoposide); ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine); doxorubicin and cyclophosphamide; gemcitabine and oxaliplatin

multidisciplinary meetings. The diagnosis of γδ T-cell lymphoma was excluded by the presence of a clonal rearrangement of the T-cell receptor β and/or histological and immunohistochemical features ($CD8^+CD56^-CD30^-$granzyme$B^+TiA1^+\beta F1^+$T-cell receptor δ^-). HPS was defined according to the hemophagocytic lymphohistiocytosis 2004 criteria.[7] HPS was considered severe if patients required intensive care and/or had severe cytopenias (hemoglobin, <6 g/dL; platelets, <50 g/L; neutrophils, <0.5 g/L).

Twenty-seven cases have been previously reported[2]; follow-up was updated.

DNA was extracted from formalin-fixed paraffin-embedded tumor tissue (n = 39), peripheral blood (n = 11), or both (n = 3), using the QIAamp DNA-formalin-fixed paraffin-embedded tissue kit or BloodMiniKit, 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 polymerase chain reaction products were bidirectionally sequenced on an ABI 3730XL DNA Analyzer (Applied Biosystems). Primers and polymerase chain reaction conditions are available on request. TIM-3 expression was studied by immunohistochemistry (anti-human TIM-3 antibody, CST 45208, Cell Signaling Technology).

Of 70 patients, 55 were women. Median age was 42 years (range, 1-90 years). Twenty-five patients (36%) had a history of autoimmune disease (13 with systemic lupus erythematosus). Thirteen patients had a previous history of panniculitis (9 with lupus panniculitis). Eleven cases displayed histological similarities with lupus erythematosus. Autoantibodies were frequently detected (62%), especially anti-nuclear antibodies, even in patients without a diagnosis of systemic lupus erythematosus.

HPS was found in 12 patients (17%), including 5 with severe HPS. The main clinical and biological characteristics are described in Table 1 and detailed in supplemental Table 1, available on the *Blood* Web site.

The median follow-up was 35 months (range, 5 days-22 years). Of 67 patients with follow-up data, 49 (73%) were in complete

Table 2. Comparison of patients with mutant and wild-type HAVCR2

	HAVCR2 mutated, n (%)	HAVCR2 wild-type, n (%)	*P*
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 (31)	5/40 (13)	ns
Severe HPS*	**3/13 (23)**	**0/40 (0)**	**.02**
Auto-antibodies	5/8 (63)	16/31 (52)	ns
Polychemotherapy	**8/12 (67)**	**5/39 (13)**	**.01**
To achieve CR	**5/10 (50)**	**3/31 (10)**	**.04**
Immunosuppressors	9/13 (69)	33/40 (83)	ns
To achieve CR	5/10 (50)	27/31 (87)	ns
Stem cell transplant	**4/13 (31)**	**1/40 (3)**	**.02**
Autologous	3/13 (23)	1/40 (3)	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

Bold indicates significant values.

F, female; M, male; ns, not significant; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.

response (CR), 5 were in partial response, and 8 had progressive disease. Five patients died: 1 from disease progression and HPS, 3 in CR, and 1 in partial response. The median duration of CR was 29.7 months (range, 0-22 years). Twenty-one patients relapsed during the follow-up (31%).

Most patients (76%) received immunomodulatory drugs as first-line treatment (corticosteroids and/or low-dose methotrexate in most cases; ciclosporin, hydroxychloroquine, chloraminophene, and α-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 vs 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.

Of 53 patients with available suitable material for Sanger sequencing, a biallelic HAVCR2 mutation was detected in 13 cases (25%). Half of the patients harboring mutations originated from East Asia or Polynesia, 1 from Réunion, and 2 from North Africa. All patients with Asian or Polynesian ancestry harbored the homozygous p.Tyr82Cys HAVCR2 variant, whereas the 3 patients with European ancestry, 1 patient from North Africa, and the patient from Reunion Island harbored the homozygous p.Ile97Met variant. The second patient from North Africa was compound heterozygous (p[Tyr82Cys]+[Ile97Met]; supplemental Table 2). Table 2 summarizes the clinical, pathological, and biological findings between the HAVCR2 mutated and wild-type groups.

In patients harboring HAVCR2 mutations, HPS was more frequent (4/13 vs 5/40) and significantly more severe (3/13 vs 0/40; $P = .02$), and polychemotherapy was significantly more often used (8/12 vs 5/39; $P = .01$). Five patients achieved CR only after intensive treatment (5/10 vs 3/31; $P = .04$); for 3 of them, polychemotherapy was used after failure of immunomodulatory treatment. The use of HSCT was significantly more frequent in patients with mutations (4/13 vs 1/40; $P = .02$). 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 patients harboring mutations and wild-type patients.

In patients harboring mutations, TIM-3 immunohistochemistry staining was cytoplasmic and paranuclear, without membrane

staining, whereas it was cytoplasmic and membranous in wild-type cases (supplemental Figure 1).

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 compared with the EORTC study could be linked to the growing use of immunomodulatory drugs as first-line treatment.[2,3]

The prevalence of HAVCR2 mutations in our study was significantly lower than in the recently published Asian SPTCL study[6] (25% vs 85%), which is consistent with the higher prevalence of the p.Tyr82Cys minor allele frequency in East Asians (0.02 vs 0.003).[5] All Asian patients with mutations harbored the p.Tyr82Cys variant; in contrast, 6 of our patients harbored the p.Ile97Met variant. 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, including patients of Asian and North African descent. The rare patients with an HAVCR2 mutation and severe HPS required intensive treatment with chemotherapy with or without 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 provide additional support that SPTCL is characterized by a good overall prognosis and can be treated with immunomodulatory drugs as first-line treatment. However, some cases have a severe presentation and require aggressive treatments. These cases are significantly associated with HAVCR2 mutations; therefore, patients with associated HPS should be screened for these mutations.

Authorship

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A complete list of the members of the French Cutaneous Lymphoma Group appears in the supplemental appendix.

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Footnotes

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For original data, please e-mail the corresponding author.

The online version of this article contains a data supplement.

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