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SHORT REPORT

Angioimmunoblastic T-cell lymphoma and Kaposi sarcoma: A fortuitous collision?

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Angioimmunoblastic T-cell lymphoma and Kaposi sarcoma: A fortuitous collision?

Aims: Follicular helper T-cell (TFH) lymphoma of the angioimmunoblastic-type (AITL), one of the most prevalent T-cell lymphomas, typically encompasses proliferation of high endothelial venules and Epstein–Barr virus-positive immunoblasts, but neither infection with HHV8 nor association with Kaposi's sarcoma (KS) have been described. The aims of this study are to characterise the association between AITL and HHV8 infection or KS.

Methods and results: Three male patients aged 49–76 years, HIV-negative, with concurrent nodal involvement by AITL and KS, were identified from our files and carefully studied. Two patients originated from countries where endemic KS occurs, including one with cutaneous KS. The lymphomas featured abundant vessels, expanded follicular dendritic cells and neoplastic TFH cells [PD1+ (three of three), ICOS+ (three of three), CXCL13+ (three of three), $CD10^+$ (two of three), BCL6 (two of three)] but lacked EBV+ immunoblasts. The foci of KS consisted of subcapsular proliferations of ERG+, $CD31^+$ and/or $CD34^+$, HHV8+ spindle cells. High-throughput sequencing showed AITL-associated mutations in *TET2* (three of three), *RHOA* (*G17V*) (three of three) and *IDH2* (*R172*) (two of three), which were absent in the microdissected KS component in two cases. Relapses in two patients consisted of AITL, without evidence of KS. No evidence of HHV8 infection was found in a control group of 23 AITL cases.

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Conclusion: Concurrent nodal involvement by AITL and KS is rare and identification of both neoplastic components may pose diagnostic challenges. The question of whether the association between AITL and KS may be fortuitous or could reflect the underlying immune dysfunction in AITL remains open.

Keywords: angioimmunoblastic T-cell lymphoma, collision, HHV8, high-throughput sequencing, Kaposi's sarcoma

Introduction

Angioimmunoblastic T-cell lymphoma (AITL), now classified as one subtype of follicular helper T-cell lymphoma (TFHL),[1,2] represents one of the most frequent peripheral T-cell lymphomas (PTCL).[3–5] It is described as an atypical polymorphous lymphoproliferative disorder with distinctive characteristics, including expanded follicular dendritic cell (FDC) meshworks, hyperplastic venules and the presence of B immunoblasts. Documentation of T-cell clonality has established the neoplastic nature of this clinically malignant disease, recently further supported by the finding of recurrent somatic mutations in the epigenetic regulators *TET2*,[6,7] *IDH2*[8,9] and *DNMT3A*,[10] often associated with a hot-spot mutation of *RHOA* (G17V).[11–14]

Kaposi's sarcoma (KS) is a rare angioproliferative disease, caused by the human herpes virus 8 (HHV8)/Kaposi's sarcoma-associated herpesvirus (KSHV), usually occurring in the context of immune deficiency. The four forms of KS – classic (Mediterranean), endemic (African), epidemic (HIV/AIDS-associated) and iatrogenic (transplant-related) – have distinct epidemiological and clinical presentations. The disease can affect every organ system, but primary involvement of lymph nodes (LN) is uncommon.[15–17]

In the 1980s, there were reports of HIV-positive patients with coexisting KS and 'angioimmunoblastic lymphadenopathy', which referred to forms of atypical reactive lymphoproliferations in untreated HIV-infected individuals.[18–22] Here, we describe three HIV-negative patients with concurrent nodal involvement by AITL and KS, an association not hitherto documented.

Materials and methods

The clinical histories, laboratory and imaging data of the three patients were collected, routinely processed biopsy materials were reviewed[1,2] and used for additional molecular analyses. In addition, 23 cases of AITL retrieved from the pathology files of the two contributing institutions (Henri Mondor University Hospital, Créteil, France) and University Hospital Lausanne (CHUV) (Lausanne, Switzerland) were used for HHV8 immunohistochemistry. Methods for immunohistochemistry,[23–25] clonality studies[26,27] and high-throughput sequencing (HTS)[24,28,29] are detailed in Supporting information, Appendix S1.

This study was performed according to the Helsinki declaration, the recommendations of the Commission cantonale d'éthique de la recherche sur l'être humain [Cantonal Commission for Ethics in Research on Human Beings] (CER-VD) and was approved by the ethic committees of the TENOMIC program (Comité de Protection des Personnes Ile-de-France IX 08-009) [Committee for the protection of people 'Ile-de-France IX'].

Results

The clinical, pathological and molecular findings are summarised in Table 1. The three patients were males aged 76, 49 and 70 years: one Caucasian, one African and one Comorian, with no notable preceding medical history, except for a haemorrhagic brain stroke in patient 3. All presented with B symptoms, generalised lymphadenopathy, anaemia and had negative HIV serology. Patients 1 and 2 also had elevated lactate dehydrogenase levels and polyclonal hypergammaglobulinaemia. Cutaneous manifestations were a skin rash (patient 1), prurit (patient 2) and a chronic foot wound clinically considered as filiariasis (patient 3).

HISTOPATHOLOGICAL AND IMMUNOPHENOTYPICAL FEATURES

The initial LN biopsies in the three patients (Figure 1) comprised a diffuse polymorphic proliferation with extracapsular extension beyond open sinuses, a diffuse vascular proliferation and a focal to marked proliferation of CD21 and/or CD23 positive FDCs. The infiltrate was composed of small lymphocytes,

Table 1. Summary of clinical, pathological and molecular/genetic findings

Case	Clinical information	Biopsies and diagnoses	Main pathological features	TR clonality assays	High-throughput sequencing[§] Tissue component(s)	Gene	Mutation[¶]	VAF
Case 1 M/76 Causasian (Switzerland)	Diagnosis: B symptoms (sweat), polyADP, skin rash, pleural effusions Stage IV; R-CHOP (6 cycles), > CR	Sample 1a: Inguinal LN: AITL & KS*	AITL: clear cells, $CD2^+CD3^+CD5^+CD7^{+/-}CD4^+/CD8^-CD10^+$ BCL6+ PD1+ CXCL13+ ICOS+, focal FDC expansion (CD21/CD23), polymorphic background, vascular hyperplasia, EBV−[†]KS: ERG+ LANA-1+, $CD34^+$	Clonal TRG and TRB	Whole LN (AITL & KS)	RHOA IDH2 TET2 TET2 TET2	c.50G>T (p.G17V) c.514A>G (p.R172G) c.3765C>G (p.Y1255*) c.3499dup (p.R1167Kfs*7) c.4661_4664del (p.T1554Sfs*16)	3% 3% 4% 4% 2%
		Sample 1b: BM: negative for AITL*	Minor T and B cell infiltrates	Polyclonal TRG and TRB	Haematopoietic tissue	TET2	c.4661_4664del (p.T1554Sfs*16)	2%
	Relapse (7 months): PolyADP, skin lesions, bendamustine, romidepsin, gemcitabine DOD (30 months)	Sample 1c: LN: AITL	LN: slight increase in density of tumour cells, idem 1st biopsy, EBV−	ND	ND	ND		
		Sample 1d: Skin: AITL	Skin: perivascular atypical lymphocytes, idem except no FDC and CD10 NI, EBV−	Clonal TRG and TRB	ND	ND		
Case 2: M/49 African Cameroun)	Diagnosis: B symptoms, polyADP, hyperγglobulinaemia Stage IV; CHOP (8 cycles), > good clinical response	Sample 2a: Axillary LN: AITL & KS	AITL: open sinus, rare clear cells, $CD2^+CD3^+CD5^+CD7^{+/-}CD4^+/CD8^-CD10^+$BCL6+PD1+CXCL13+ ICOS+, FDC expansion (CD21/CD23), polymorphic background, vascular hyperplasia, EBV-KS: ERG+ LANA-1+ $CD34^+$	Clonal TRG (TRB ND)	AITL area (microdissected)	RHOA TET2 TET2 PLCG1	c.50G>T (p.G17V) c.3955-2A>G (splice site) c.2290dup (p.Q764Pfs*5) c.3506A>G (p.D1169G)	5% 5% 5% 4%
	Relapse (8 months): PolyADP 5-azacytidine (8 courses), > good clinical response Relapse (17 months): Vinblastine + allogeneic bone marrow transplantation, > CR, ANED (44 months)	Sample 2b: Cervical LN: AITL	Open sinus, rare clear cells, $CD2^+CD3^+CD5^+CD7^{+/-}CD4^+/CD8^-CD10^-$BCL6-PD1+CXCL13+ ICOS+, FDC expansion (CD21/CD23), polymorphic background, vascular hyperplasia, EBV+[‡]	Clonal TRG (TRB ND)	AITL ([§])	RHOA TET2	c.50G>T (p.G17V) c.3955-2A>G (splice site)	4% 8%
		Sample 2c: Nasopharynx: AITL		Clonal TRG (TRB ND)	AITL ([§])	RHOA TET2	c.50G>T (p.G17V) c.3955-2A>G (splice site)	5% 6%

Table 1. (*Continued*)

Case	Clinical information	Biopsies and diagnoses	Main pathological features	TR clonality assays	High-throughput sequencing[§]			
					Tissue component(s)	Gene	Mutation[¶]	VAF
Case 3: M/70 Comorian (Mayotte)	Diagnosis: B symptoms, polyADP, anaemia, thrombopenia, hypergammaglobulinaemia, cutaneous wound Stage IV; palliative care (lost to follow-up)	Sample 3a: Inguinal LN: AITL & KS	AITL: clear cells, $CD2^+$ $CD3^+$ $CD5^+$ $CD7^+$ $CD4^+/CD8^-CD10^-BCL6^-$PD1+ CXCL13+ ICOS+ IDH2R172K+, FDC expansion (CD21/CD23), polymorphic background, vascular hyperplasia, EBV-KS: ERG+ LANA-1+ $CD34^+$	Clonal TRG (TRB ND)	AITL area (microdissected)	RHOA IDH2 TET2 TET2 TET2 DNMT3A	c.50G>T (p.G17V) c.515G>A (p.R172K) c.3277del (p.T1093Pfs*13) c.3688_3689delinsG (p.I1230Afs*23) c.2086del (p.S696Pfs*4) c.2645G>A (p.R882H)	4% 5% 12% 8% 2% 7%
		Sample 3b: Skin (foot): KS	KS: ERG+ LANA-1+ $CD34^+$	ND	KS ([§])	No mutation detected		

AITL, TFH lymphoma, angioimmunoblastic-type; ANED, alive with no evidence disease; CR, complete remission; DOD, dead of disease; FDC, follicular dendritic cells; idem, identical; ISH, *in-situ* hybridisation; KS, Kaposi sarcoma; LN, lymph node; M, male; ND, not done; NI, not interpretable; PolyADP, polyadenopathy; VAF, variant allele frequency.

*In patient 1, nodules of cyclin D1+ SOX11− B lymphocytes with clonal IGH gene rearrangement were present in the initial LN biopsy (sample 1a), consistent with a concurrent mantle cell neoplasm, whereas a $CD5^-$ monoclonal B cell lymphocytosis was evidenced in the bone marrow (sample 1b).

[†]Rare EBER+ small lymphocytes.

[‡]In patient 2, scattered (lymph node, sample 2b) to numerous (nasopharynx, sample 2c) EBV-positive cells were seen at relapse, whereas cells positive for EBV by EBER *in-situ* hybridisation were absent on the initial LN biopsy (sample #2a).

[§]All data presented here were obtained with a 26-gene panel on a MiSeq sequencer, except for the samples indicated by ([§]), which were investigated with a nine-gene panel relevant for TFH lymphomas on a PGM sequencer.

[¶]Reference transcripts: *RHOA* NM_001664.3, *IDH2* NM_002168.3, *TET2* NM_001127208.2, *DNMT3A* NM_022552.4, *PLCG1* NM_182811.1.

histiocytes, scattered eosinophils and plasma cells (abundant in cases 1 and 3) and a minor component of small/medium atypical lymphoid cells, with distinctive clear cell cytomorphology in cases 1 and 3. The atypical lymphoid cells were $CD3^+$, $CD2^+$, $CD5^+$ and $CD4^+$, with partial loss of CD7 (cases 1 and 2) and expression of several TFH markers (PD1+, CXCL13+ and ICOS+ in all cases, $CD10^+$ and BCL6+ in two cases). In case 3, they were also IDH2R172K+. $CD20^+$ blasts were few or scant. EBER *in-situ* hybridisation highlighted rare EBER-positive small lymphocytes in case 1 and was negative in the other two. Besides the typical AITL areas, the LNs comprised several sharply demarcated capsular, subcapsular or perivascular compact foci of spindle cells arranged in short, incurvated fascicles and delineating narrow vascular spaces, associated with a plasma cell infiltrate. These KS foci were positive for ERG, LANA-1 and CD34 and/or CD31. No HHV8 staining was observed in lymphoid or endothelial cells outside the areas of KS and no TFH cell infiltrate was noted in the KS. The biopsy of the cutaneous foot lesion in patient 3 showed only HHV8-positive KS.

Of note, no HHV8-positive staining was found in the 23 other consecutive AITL LNs used as controls.

In patients 1 and 2, subsequent biopsies (from lymph node, nasopharynx and skin) obtained at clinical relapses all showed involvement by AITL, with no evidence of KS and no detectable expression of HHV8 antigens by IHC.

MOLECULAR FINDINGS

The initial LN from the three patients harboured monoclonal TR gene rearrangement(s). Sequential biopsies from patients 1 and 2 (LN and nasopharynx) with AITL showed similar clonal TR gene rearrangements. Clonality was not detected in the cutaneous KS in patient 3.

HTS analysis, using a 26-gene PTCL panel performed on the bulk tumour (patient 1) or on microdissected AITL areas (patients 2 and 3), showed two or three *TET2* mutations and *RHOA* (G17V) variant in all cases. Additional mutations were found in *IDH2* (R172G) (patient 1), *PLCG1* (patient 2) *IDH2* (R172K) and *DNMT3A* (patient 3). In contrast, no mutation was detected in the KS areas microdissected from the LNs and analysed separately in patients 2 and 3 or in cutaneous KS in patient 3. Variant allelic frequencies ranged from 3 to 5% for *RHOA* or *IDH2* mutations, and from 2 to 12% for *TET2* mutations. No novel mutations were observed in the LN and nasopharyngeal relapses of patient 2 using a smaller nine-gene HTS assay, but one of the *TET2* mutations and the *PLCG1* mutation identified at diagnosis were no longer detected, although technically covered by the panel.

Discussion

We report here three patients with simultaneous diagnoses of AITL and Kaposi sarcoma co-localised in lymph node biopsies, a type of collision tumour hitherto not described, to our knowledge.

The clinical presentation of elderly patients with generalised lymphadenopathy and B symptoms, the typical pathological features and the characteristic mutational pattern combining *RHOA* (G17V) and *TET2* mutations supported the diagnosis of AITL.[3,11–13,29] Moreover, two cases carried an *IDH2* R172 mutation, a genetic mark almost specific of AITL[8,9] reportedly associated with clear cell cytomorphology[29,30] and confirmed in our cases.

The foci of KS located in or beneath in the capsule of the lymph node accounted volume-wise for a minor component of the lymphadenopathy. LN involvement was the only disease site and a fortuitous histological discovery, besides AITL in patients 1 and 2. The context of patient 3 was different, with clinically overt cutaneous KS and secondary nodal extension.

The demonstration that the AITL-associated *TET2* mutations, known to occur in precursor haematopoietic cells,[11,12] was found only in the AITL but absent in the KS compartment in the two cases investigated by microdissection supports two genetically unrelated diseases. The TFH lymphoma and vascular neoplasms were adjacent but sharply demarcated, with no HHV8 staining observed either in the hyperplastic venules or in the B blasts of AITL. This contrasts with the observation of KSHV infection in both plasmablasts and endothelial cells in patients with concomitant multicentric Castleman's disease and KS.[31,32]

The synchronous occurrence of two rare diseases in the same anatomical site raises the question of a purely fortuitous association versus a mechanistic link or common predisposing conditions. A fortuitous co-occurrence may be supported by the fact that the KS could be regarded as endemic in two patients originating from Africa.[33,34] In contrast to EBV detected in the B immunoblasts in up to 80% of AITLs,[2,3,35,36] HHV8 infection has not been reported as a feature of AITL. Interestingly, however, in a recent high-throughput transcriptomic viral analysis of PTCLs,[37]

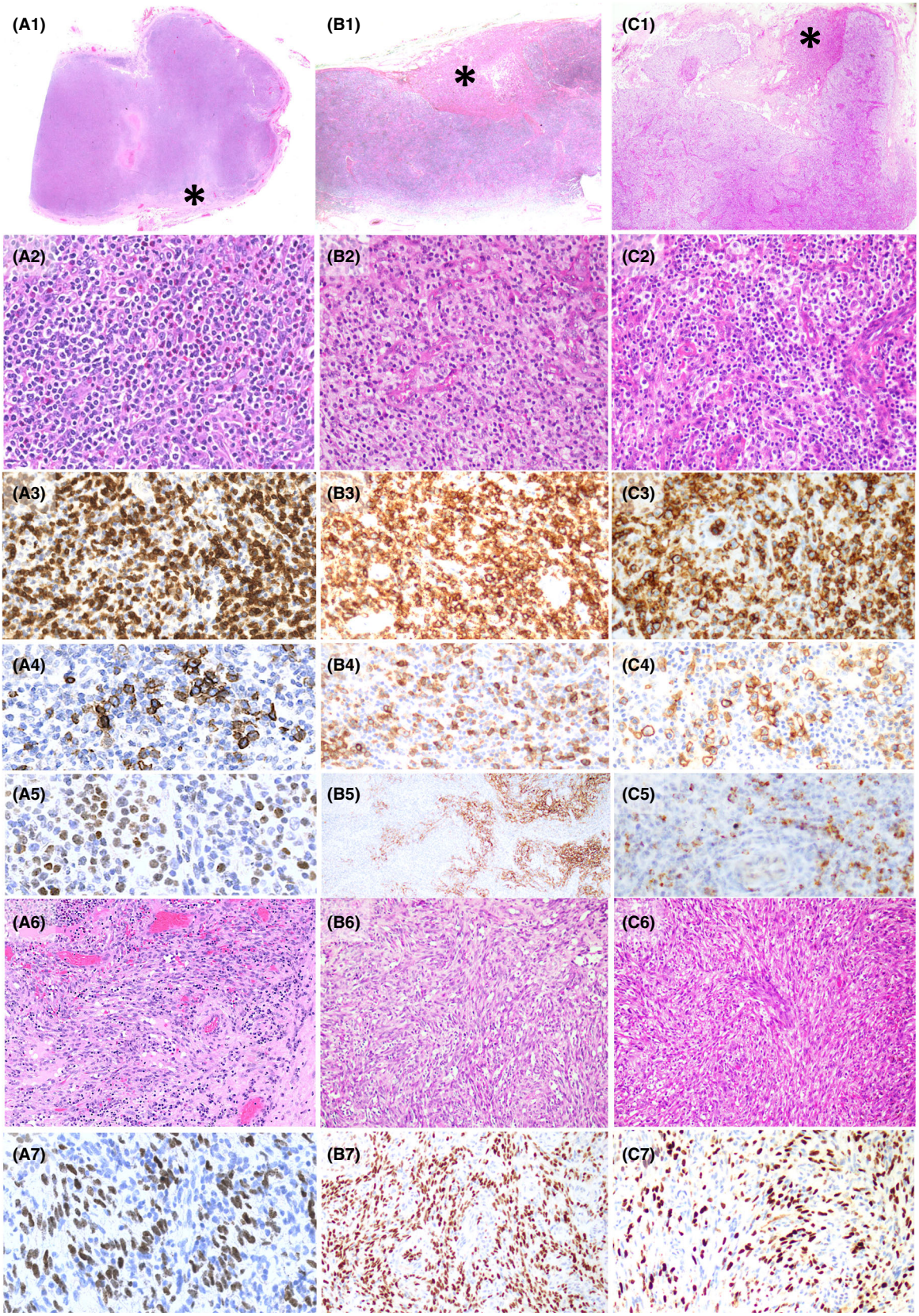

Figure 1. Pathological features of the diagnostic lymph node biopsy in patients 1 (**A**), 2 (**B**) and 3 (**C**). At low-power view (**A1–C1**, H&E stain), the three lymph nodes were characterised by a diffuse lymphoproliferation obliterating their architecture; *denote more solid subcapsular foci corresponding to the Kaposi sarcoma proliferation; note that in patient 1 (**A1**) the Kaposi sarcoma infiltrate was subtle and only seen at higher magnification, and there was a small focus of necrosis. At higher magnification (**A2–C2**, H&E stain), the lymphoproliferation comprises atypical lymphoid cells with clear cytoplasm that were particularly prominent in case 3 (**C2**) admixed with a few immunoblasts and eosinophils and hyperplastic venules. In selected immunostains, in patient 1 the majority of lymphoid cells are positive for CD3 (**A3**), a subset is positive for ICOS (**A4**) and many are positive for BCL6 (**A5**); in patient 2, the majority of lymphoid cells are positive for CD2 (**B3**), many are positive for PD1 (**B4**) and CD21 highlights expanded follicular dendritic cell meshworks (**B5**); in patient 3, the majority of lymphoid cells are positive for CD2 (**C3**), many are positive for ICOS (**C4**) and an antibody directed against IDH2 R172K produces granular cytoplasmic staining in atypical clear cells (**C5**). **A6–C6** show the fusiform cell proliferation foci (H&E stain) which were positive by immunohistochemistry for LANA-1 (**A7–C7**).

HHV8 reads were identified in two of 18 AITL cases. Nevertheless, the fact that 16 of 18 AITL cases in that study did not contain reads of HHV8, and that 23 AITL cases tested by immunohistochemistry were negative for LANA-1, confirm that the presence of HHV8-infected cells in AITL is rare if not exceptional. It could be speculated that HHV8 infection could be favoured by the immune dysfunction commonly reported in AITL patients.[35,38] Indeed, TFH cells produce various immunosuppressive cytokines, such as TGF-β and IL-10. Conversely, HHV8 infection of endothelial cells may induce the production of cytokines such as vIL-6,[31] which could favour the TFH growth or differentiation.[38–40] Another mechanism to consider is that VEGF and its receptor, both expressed by neoplastic TFH cells and endothelial cells in AITL,[41] could sustain the proliferation of HHV8+ endothelial cells and KS development. Interestingly, none of the three KS-associated AITLs contained EBV-positive B blasts, questioning whether HHV8 could have substituted to EBV to support the TFH component in these cases.

Whether coincidental or related, the rare association of AITL and KS could constitute a diagnostic pitfall: on one hand, the AITL in patient 3 could have been missed if only the skin biopsy had been examined; on the other hand, the KS component could have been missed in the patients where the AITL component was predominant. The clinical relevance of such an association remains to be determined. In this small series, two of the three patients relapsed with lymphoma, but no KS was found in sequential biopsies.

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Author contributions

E.P., D.M., L.dL., P.G. performed study design, analysed data and wrote the paper. E.P., D.M., P.D., V.F., A.L., B.B., M.H.D6L, provided patient samples, made pathological review or collected data. A.L., B.B., A.D., F.L., C.R., A.D., N.S. provided analysis and interpratation of HTS data. F.L., N.K., P.C., provided clinical information. V.F., M.H.D-L. provided technical support and performed experiments. All authors read and approved the final paper.

Conflicts of interest

The authors declare no competing financial interests.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplemental information.