Treatment of MKL-1 cells with selinexor resulted in a dose-dependent reduction of both LTA and STA protein expression. Furthermore, a reduction in XPO1 protein expression was detected even at the lowest selinexor dose, although this downregulation did not demonstrate a dose response in the MKL-1 cells (Figure 1a). Treatment of MS-1 cells resulted in similar results, with nearly complete ablation of viral protein production at the higher selinexor doses tested. Furthermore, a reduction in XPO1 protein expression was detected, but this was dose-dependent in MS-1 cells (Figure 1b). The IC_{50} values determined by cell proliferation assay were 7·85 nmol L^{-1} for MKL-1 cells and 85·72 nmol L^{-1} for MS-1 cells.

XPO1 inhibitors demonstrate antiviral activity against an array of viruses, including influenza A, influenza B and severe acute respiratory syndrome coronavirus.[5,6] While our study was conducted *in vitro*, the results demonstrate that XPO1 inhibitor treatment can efficiently downregulate MCPyV viral oncoprotein expression in MCC cell lines. This illustrates that there is promise in using XPO1 inhibitors for MCPyV-associated MCC management. The downregulation of STA expression is particularly striking because STA is capable of inducing oncogenesis alone.[1] Differences in the dose of selinexor needed to achieve LTA and STA protein ablation between the MCPyV-positive cell lines tested suggest some MCCs may be more vulnerable to this treatment than others. In addition, the decrease in XPO1 expression after selinexor treatment may represent a therapeutic advantage independent of LTA and STA expression inhibition. XPO1 is frequently overexpressed or mutated in a variety of viral and nonviral-associated malignancies, and XPO1 expression is often associated with poor prognosis in these cancers, although the association with MCC has not been established.[7]

Tumour-targeted therapies such as selinexor represent a growing treatment modality for MCC. A previous study by Akaike *et al.* examining the use of somatostatin analogues to treat metastatic MCC with high somatostatin receptor expression found that these receptor analogues led to clinically significant disease control.[8] Taken together, our results demonstrate that evaluating MCC tumour-targeted therapies must continue. Such agents may be used in combination with the standard of care (e.g. immunotherapies) and may have more favourable side-effect profiles than traditional chemotherapies.[8] Future studies are warranted in exploring the importance of XPO1 in MCC and investigating the use of XPO1 inhibitors *in vivo* and in combination with other therapies.

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COVID-19-associated cutaneous manifestations: does human herpesvirus 6 play an aetiological role?

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Dear Editor, Recently, during the development of the coronavirus disease 2019 (COVID-19) pandemic, several publications have warned of possible cutaneous manifestations in association with this novel coronavirus (SARS-CoV-2). In our hospital, we have created a multidisciplinary unit with a specific protocol to attend to patients with these manifestations.

For this study, we included patients who, during the development of the pandemic, were clinically suspected and/or microbiologically confirmed to have COVID-19 and also had a recent-onset skin rash (within the last 4 weeks). All patients underwent biochemistry, haematimetry and serology for parvovirus B19 and for human herpesvirus (HHV)-6, in addition

Table 1 Characteristics of the patients with positive serology for human herpesvirus (HHV)-6

Patient no.	Sex, age (years)	Medical history	Clinical pattern	Location	Symptoms suggestive of COVID-19	COVID-19 test[a]	HHV-6 serology	Coagulation study[b]	Histology	Other findings
1	F, 14	–	Perniosis-like	Feet	Fever	Negative (serology)	IgM+, IgG+	–	–	
2	M, 4	–	Perniosis-like	Hands and feet	Fever	Negative (PCR, serology)	IgG+ (seroconversion)	Normal	–	Brother with the same symptoms
3	M, 32	HIV	Maculopapular	Trunk, UP, LE, hands, palms or soles, mucous, genitals	Dyspnoea, general malaise/ myalgia/ asthaenia	Negative (serology)	IgM+, IgG+	–	Vacuolar interface dermatitis and inflammatory perivascular and interstitial infiltrate	Suspicion of toxicoderma owing to recent change of antiretroviral
4	M, 33	–	Maculopapular, pityriasis rosea-like	Trunk, UP, LE, hands, feet, palms and soles, head	–	Negative (PCR, serology)	IgM+, IgG+	–	Vacuolar interface dermatitis with keratinocyte necrosis	Syphilis serology: negative
5	F, 29	–	Livedoid	UP, LE, hands, feet	Fever, myalgia, headache	Negative (PCR, serology)	IgM+, IgG+	Normal	Dermal oedema and ectasia of the superficial plexus capillaries	
6	F, 4	–	Vesicular	Trunk, UP, LE, head, mucous	Fever, digestive symptoms[c]	Negative (serology)	IgM+, IgG+	–	–	VZV: IgG+, IgM− (vaccinated)
7	M, 50	–	Maculopapular	UP, LE	–	Negative (serology)	IgM+	–	–	
8	M, 3	–	Perniosis-like	Hands	Fever, digestive symptoms	Negative (serology)	IgM+, IgG+	Normal	–	Sister with same symptoms and inflammation and erythema of the helix
9	F, 48	–	Maculopapula and seborrhoeic dermatitis	Trunk, UP, head	Fever, general malaise/myalgia/ asthaenia, headache, anosmia/ageusia	Positive PCR of nasopharyngeal swab, serology IgG+	IgM+, IgG+	–	–	
10	F, 50	SLE	Worsening of SCLE	Trunk	General malaise/ myalgia/asthaenia, anosmia/ageusia	Positive PCR of nasopharyngeal swab	IgM+, IgG+	Normal	Interface dermatitis consistent with SCLE	
11	M, 49	Knee arthroscopic surgery with osteosynthesis material	Urticarial	Trunk, UP, LE, head	Fever, dyspnoea	Serology IgM+ (with negative PCR and without seroconversion)	IgM +, IgG+	–	Urticaria vasculitis	Normal complement levels
12	F, 45	Bronchial asthma	Maculopapular, erythema multiforme-like	Trunk, UP, LE	Fever, dyspnoea, general malaise/ myalgia, digestive symptoms	Positive PCR of nasopharyngeal swab, serology IgG+	IgM+, IgG+	–	–	

M, male; F, female; UP, upper extremities; LE, lower extremities; PCR, polymerase chain reaction; VZV, varicella zoster virus; SLE, systemic lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus. [a]Kit, S/S. [b]International normalized ratio, prothrombin time, cephalin time, activated partial thromboplastin time, partial thromboplastin time, derived fibrinogen, D-dimer, lupus anticoagulant, anticardiolipin, anti-beta-2 glycoprotein, antithrombin III, homocysteine and protein C and S. [c]Nausea, vomiting, diarrhoea.

to other serologies and a coagulation study according to clinical manifestations. Based on the findings of these tests, we randomly selected 12 hospitalized patients, of a similar median age, with COVID-19 but without cutaneous manifestations, and we requested HHV-6 serology. The SARS-CoV-2 antibody assay was Roche's Elecsys® Anti-SARS-CoV-2 (Roche, Basel, Switzerland) and the HHV-6 antibody assay was ELISA-VIDITEST anti-HHV-6 IgM (Vidia, Prague, Czech Republic). The protocol was approved by the Aragon Ethical Committee for Clinical Research.

In total, 53 patients were included between 1 May 2020 and 31 October 2020. Overall, 20 (38%) patients had a positive COVID-19 test and the remaining patients had symptoms suggestive of COVID-19. Unexpectedly, 12 of 53 patients presented IgM serology and/or seroconversion to IgG of HHV-6; the other 41 patients were negative for IgM of HHV-6. Of these 12 patients, only four (33%) tested positive for SARS-CoV-2 [for these 12 patients, the median delay between first symptoms and polymerase chain reaction (PCR) or serology was 3 days and 27·5 days, respectively]. Characteristics of these patients are summarized in Table 1. In the COVID-19 control group, two patients had positive IgM for HHV-6. Statistical analysis performed using Pearson's χ^2-test did not show significant differences between the proportion of patients who were positive for HHV-6 (12 of 53 vs. two of 12) in both groups ($P = 0{\cdot}64$). For the same period of the previous year, 175 HHV-6 IgM serologies were requested, of which only three were positive (all three in children).

Galván Casas *et al.* described the following five clinical patterns of cutaneous manifestations associated with SARS-CoV-2: acral areas of erythema with vesicles or pustules (pseudochilblain), other vesicular eruptions, urticarial lesions, maculopapular eruptions and livedo or necrosis.[1] Various hypotheses about the mechanisms inducing the different cutaneous lesions have been proposed. These include immunological responses, hypercoagulability state, drug reactions, a direct cytopathic effect of SARS-CoV-2 or the role of the receptor of SARS-CoV-2, i.e. angiotensin-converting enzyme 2, which was found to be expressed on the skin, mainly on keratinocytes.[2] Alternatively, the role of other viruses, particularly those belonging to the Herpesviridae family,[2] has been suggested, especially in vesicular eruptions, erythema multiforme lesions and pityriasis rosea.[3,4] In fact, recent reports refer to the increase in frequency of pityriasis rosea after the occurrence of the COVID-19 pandemic.[4,5] In one case the reactivation of HHV-6 was demonstrated by PCR,[3] and a case of coreactivation of herpes simplex virus 1 and varicella zoster virus in a critically ill patient with COVID-19 was also reported.[6] In this regard, we want to highlight the finding of positive IgM serology for HHV-6 in our series of patients. Cutaneous diseases that have been associated with HHV-6 infection include roseola infantum, pityriasis rosea, Gianotti–Crosti syndrome, drug reaction with eosinophilia and systemic symptoms or thrombocytopenic purpura, among others.[7] Nevertheless, an aetiological association between HHV-6 infection and a cutaneous disease is complicated by the ubiquity and nearly universal prevalence of the virus. In addition, several samples over time are needed to demonstrate seroconversion, which is considered an indispensable requirement to prove the active pathological role of the virus.[7] However, serology as a diagnostic procedure has disadvantages and limitations, such as a lack of interpretation for the diagnosis of reactivations or cross-reactivity with other betaherpesviruses.[8] As our patients do not share clinical characteristics, and the difference in the proportion of both groups is not statistically significant, it is very difficult to be sure that HHV-6 has played an aetiological role in the development of cutaneous manifestations. However, it is even more difficult to attribute cutaneous manifestations to SARS-CoV-2 given the negative results of several microbiological tests, even repeatedly, in some of these patients. Thus, we want to emphasize the finding of a positive serology for HHV-6 in different clinical patterns described in association with COVID-19. We suggest that SARS-CoV-2 could cause the reactivation of other viruses, such as HHV-6, which could be responsible for some cutaneous manifestations initially related to COVID-19. The main limitation of our study is that only 38% of the patients were positive for SARS-CoV-2 (33% in the HHV-6 group). Therefore, more studies are necessary to demonstrate the association between SARS-CoV-2 and HHV-6, and its possible aetiological role in COVID-19-associated cutaneous manifestations.

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Identification of compound heterozygous mutations in *AP1B1* leading to the newly described recessive keratitis–ichthyosis–deafness (KIDAR) syndrome

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Dear Editor, Recently, mutations in adaptor-related protein complex 1 subunit beta 1 (AP1B1) have been identified as the cause of a new form of syndromic ichthyosis, which is characterized by neonatal onset of ichthyosis, erythroderma and deafness accompanied by failure to thrive and developmental delay.[1,2] In adulthood, keratitis has been diagnosed as well.[1] Based on the observed phenotype and the autosomal recessive mode of inheritance, the disease has been classified as a keratitis–ichthyosis–deafness syndrome (KIDAR; OMIM 242150). In this letter, we describe an additional case of KIDAR caused by *AP1B1* mutations, including one novel missense mutation. We also show the molecular consequences of the mutations and define the main features of this new syndrome.

The girl was born at term without a collodion membrane or persisting dryness of skin. At the age of 2 weeks, she developed an ichthyosiform erythroderma and chronic, severe pruritus (Figure 1a). Global developmental retardation and failure to thrive were observed, as well as thickened plantar surface (Figure 1b), bilateral ectropion and partial alopecia. The nails were unremarkable. Her complete blood count with differential, serum very long-chain fatty acids, and serum levels of iron, zinc, copper and ceruloplasmin were normal. At the age of 31 months (Figure 1c), her skin was dry with generalized scaling, most pronounced on the face and the extremities, with light erythematous patches without erosions, blistering or other signs of skin fragility. Dermatological treatment consisted of frequent emollient applications and short courses of topical corticosteroids or pimecrolimus ointment. Despite chronic diarrhoea she caught up with growth retardation and showed less severe failure to thrive. Meanwhile, she had been diagnosed with bilateral deafness and had developed moderate photophobia. Other neurological, ocular or dental anomalies were not present. The histopathology of the skin biopsy presents epidermal thickening and hyperkeratosis (Figure 1d). The patient underwent extensive diagnostic investigations excluding a broad range of cutaneous and syndromal diseases potentially underlying infantile erythroderma.[3]

Whole-exome sequencing and subsequent Sanger sequencing in our patient revealed compound heterozygous mutations in *AP1B1* (c.322C>T, p.Arg108Trp and c.2254delC, p.Leu752Serfs*26) (Figure 1e), while each of the healthy, nonconsanguineous parents carried one of the variants in a heterozygous state. Five recently described cases with *AP1B1* mutations and our index patient share almost the same phenotype including ichthyosis, erythroderma, deafness and developmental delay. Both the phenotypic similarities and the c.2254delC mutation already described in this context (referred to a different transcript) support our findings that the variants detected in *AP1B1* cause the phenotype of our patient.[1,2] Severe failure to thrive and developmental delay within the first months of life seem to be compensated in later childhood.[1]

Molecular examination demonstrated complete loss of AP1B1 in the epidermis (formalin-fixed paraffin-embedded sections) and isolated keratinocytes from our patient's skin (Figure 1f, g). On the genetic level, the frameshift mutation (c.2254delC) induces a premature stop codon (p.Leu752Serfs*26) activating nonsense-mediated mRNA decay. The missense mutation (c.322C>T, p.Arg108Trp) affects a highly conserved residue (phyloP/phastCons) within the putative protein-binding region of AP1B1 (Figure 1h).[4] *In silico* analysis predicts the mutation to be deleterious (SIFT), probably damaging (PolyPhen) and disease causing (MutationTaster). Reverse-transcriptase polymerase chain reaction from isolated keratinocytes detected the missense mutation but not the frameshift mutation, confirming the presumed mRNA degradation from the allele carrying the frameshift mutation (Figure 1i). This is further supported by the presence of a homozygous

Figure 1 Clinical and histological features of our patient and molecular examination of the novel mutation. (a–c) The patient presented an ichthyosiform erythroderma, sparse hair growth and thickening of the plantar surface. (d) Histopathological examination demonstrates epidermal thickening and hyperkeratosis (bar = 25 μm). (e) Sanger sequencing demonstrates compound heterozygous mutations in *AP1B1* consisting of c.322C>T (p. Arg108Trp) and c.2254delC (p.Leu752Serfs*26). (f, g) Examination of the patient's epidermis (bar = 25 μm) and isolated keratinocytes demonstrates lack of AP1B1 protein signal. (h) The amino acid change p.Arg108Trp is located within the putative protein-binding site (light green). The frameshift mutation results in an amino acid change p.Leu752Serfs*26. (i) Sanger sequencing of cDNA exhibited the presence of mRNA carrying the missense mutation but no mRNA carrying the deletion mutation. The heterozygous single-nucleotide polymorphism c.2268G>A in genomic DNA was found to be homozygous in cDNA (blue arrowhead).