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Blanchard, Gabriela; Atallah, Isis; Blanchard, Maël; Fehrenbacher, Birgit; Schaller, Martine; Riccio Wicht, Orbicia; Ballerini, Claudia; Candotti, Fabio; Guenova, Emmanuella

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Primary cutaneous T-cell lymphoma not otherwise specified reveals a novel *RAB27A* variant in Griscelli syndrome type 2

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Dear Editor, Primary cutaneous peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is a rare and aggressive form of extranodal non-Hodgkin lymphoma. Diagnosed by exclusion, PTCL-NOS typically manifests with disseminated papules and nodules. It predominantly affects men, with a median age of diagnosis in the seventh decade of life. The prognosis of PTCL-NOS is generally poor, with a 5-year survival rate of 54%.[1]

A 47-year-old female patient was referred to our dermatology clinic with a 15-year history of diffuse erythematous infiltrated plaques and nodules, treated previously as systemic lupus erythematosus and sarcoidosis without success. Treatments with hydroxychloroquine, azathioprine, methotrexate, infliximab, rituximab and low-dose systemic corticosteroids all proved insufficient. Initial skin biopsies showed primarily sharply defined perivascular infiltrates, consisting of small lymphocytes without overt atypia, confined to the superficial dermis. While early biopsies did not provide diagnostic certainty, a clear progression was observed in the subsequent biopsies. Histology of one of the tumoral lesions subsequently revealed a dense dermal infiltrate extending into the subcutaneous fat, consisting mainly of atypical small, medium-sized and large pleomorphic CD8+ T cells with focal epidermotropism and folliculotropism. An initial positron emission tomography-computed tomography scan confirmed extensive skin disease without extracutaneous involvement at the time of diagnosis. Correlation between clinical, histological and radiological findings established the diagnosis of PTCL-NOS with an atypical, chronic disease course (Figure 1 a–c). Owing to a personal history of recurrent infections, parental consanguinity and an atypical lymphoproliferative disorder, the patient was investigated for an underlying primary immunodeficiency. Targeted exome sequencing revealed two previously unreported compound heterozygous variants in *RAB27A*: a pathogenic deletion c.514-518delCAAGC; p.Gln172AsnfsTer2 leading to a frameshift in exon 7, and a pathogenic variant c.227C > T; p.Ala76Val in exon 4, suggesting the diagnosis of Griscelli syndrome type 2 (GS2) (ORPHA 79477, OMIM 607624). The patient was referred to haematology for evaluation of eligibility for a haematopoietic stem cell transplant.

GS2 is a rare autosomal recessive disorder typically appearing in childhood. It is caused by mutations in the *RAB27A* gene, which encodes the GTP-binding protein, RAB27A. RAB27A regulates intracellular protein trafficking and plays a key role in cytotoxic granule exocytosis.[2] The interaction between RAB27A, motor protein myosin-5a and melanophilin mediates the peripheral accumulation of melanosomes in melanocytes before their transfer to the adjacent keratinocytes in hair and skin. Variants in these three proteins underlie the three Griscelli syndrome subtypes and result in a so-called diluted phenotype with partial albinism.[3] RAB27A also interacts with Munc13-4 to ensure effective cytotoxic effector function of natural killer (NK) cells and CD8 T cells.[4]

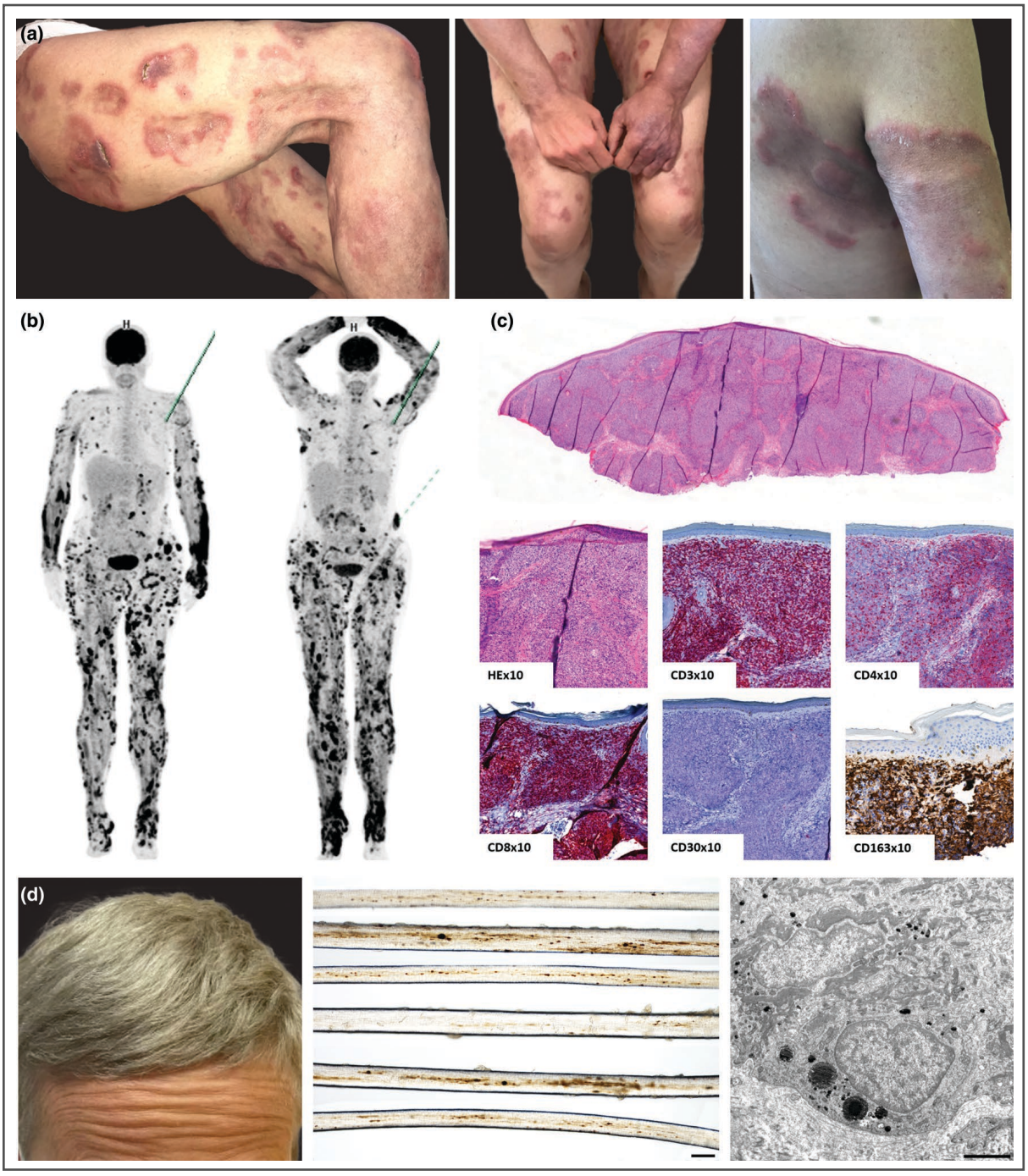

Figure 1 Clinical and histological manifestations compatible with the diagnosis of a primary cutaneous peripheral T-cell lymphoma not otherwise specified. (a) Clinical image showing multiple infiltrated erythematous plaques and nodules, some ulcerated, disseminated over the body surface. (b) Positron emission tomography-computed tomography showing an extensive skin disease without extracutaneous involvement at diagnosis. (c) Histology showing a dense dermal infiltrate extending into the subcutaneous fat, predominantly consisting of atypical small, medium-sized and large pleomorphic CD8+ T cells. Presence of a narrow band zone free of infiltrate, along with focal epidermotropism and folliculotropism. Additional stainings show numerous admixed CD163+ cells. (d) Further examination revealed the presence of silvery-grey hair since infancy with hair shaft analysis showing large melanin granules in the medullary zone and giant melanosomes in melanocytes of the skin, indicating Griscelli syndrome type 2. Scale bar = 100 μm (hair). Scale bar = 2.5 μm (melanocyte). HE, haematoxylin and eosin.

GS2 usually manifests with partial albinism, silvery hair, immunodeficiency and a predisposition for haemophagocytic lymphohistiocytosis (HLH).[5] Neurological abnormalities in GS2 are frequent and considered secondary to HLH. Further examination of our patient's personal history revealed the presence of silvery-grey hair since infancy. Light microscopy of the hair in GS2 typically shows large clusters of melanin with an irregular distribution, while electron microscopy reveals abnormal accumulation of melanosomes in melanocytes.[6] Hair shaft analysis in our

patient confirmed the presence of large, unevenly distributed clumps of pigment in the medullary zone. Electron microscopy revealed the pathological accumulation of giant melanosomes within melanocytes, further corroborating the diagnosis of GS2 (Figure 1d).

Despite multiple episodes of recurrent fever and pancytopenia, our patient has never met the criteria for HLH. While the deletion c.514-518delCAAGC; p.Gln172AsnfsTer2 in exon 7 is predicted to lead to loss of RAB27A protein, the missense variant c.227C > T; p.Ala76Val in exon 4 might result in residual RAB27A functional activity, which could explain both the delayed onset of clinically relevant disease and the absence of HLH in our patient.

In RAB27A-deficient T and NK cells, the cytotoxic machinery is compromised because lytic granules are unable to reach the immunological synapse, preventing the effective elimination of target cells. Interestingly, a few cases of lymphoma associated with variants in *RAB27A* have been previously reported. These include three cases of Hodgkin lymphoma, including an Epstein–Barr virus-associated Hodgkin lymphoma with CD30+ cells and a nodular lymphocyte predominant Hodgkin lymphoma stage IV. A case of T-cell histiocyte-rich large B-cell lymphoma, and possibly a case of immunoblastic T-cell lymphoma have also been reported.[4,7,8] Cutaneous lymphomas can now be added to the array of GS2 manifestations, emphasizing its broad clinical spectrum.

In conclusion, lymphoproliferative disorders, including cutaneous lymphomas, should be considered part of the dermatological spectrum of GS2. In addition, while diagnosis of GS2 has been made previously in adult patients who presented with HLH, our observations suggest that HLH is not an inevitable outcome of GS2 even in patients surviving into the fifth decade of life.

Gabriela Blanchard[1], Isis Atallah[2], Maël Blanchard[1], Birgit Fehrenbacher[3], Martin Schaller[3], Orbicia Riccio[4], Claudia Ballerini[4], Fabio Candotti[4] and Emmanuella Guenova[5,6]

[1]Division of Dermatology and Venereology, Geneva University Hospitals, Geneva, Switzerland; [2]Division of Genetic Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [3]Department of Dermatology, Eberhard Karls University, Tübingen, Germany; [4]Division of Immunology and Allergy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [5]Department of Dermatology and Venereology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland and [6]University Institute and Clinic for Immunodermatology, Medical Faculty, Johannes Kepler University, Linz, Austria

Correspondence: Emmanuella Guenova. Email: emmanuella.guenova@unil.ch

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Patient consent: The authors obtained written consent from patients for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

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