Nevus anemicus and RASopathies

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INTRODUCTION

Tadini and colleagues were the first to report the correlation between anemic nevi and RASopathies.[1] A retrospective study in their genodermatosis center identified anemic nevi at different anatomic sites in a cohort of neurofibromatosis type 1 (NF1) (50/565).

In 2013, Marque et al published the frequent occurrence of anemic nevi in 77 of 151 patients clinically diagnosed with NF1, but not in 7 patients with *SPRED1* (sprouty-related, EVH1 domain—containing protein 1), 2 with *PTPN11* (protein tyrosine phosphatase nonreceptor type 11), and 1 with *RAF1* (rapidly accelerated fibrosarcoma-1) mutations.[2] In a later study in 100 genetically confirmed NF1 patients, anemic nevi were found in 28 children with NF1,[3] much higher than the estimated 1%-5% in the general population.[2] Anemic nevi were suggested as an additional diagnostic marker of NF1, facilitating differentiation from other genodermatoses with café au lait macules (CALMs) and lentigines.[1-3] Anemic nevi are congenital pale macules or patches, which become more prominent by warming or rubbing of the skin and disappear with diascopy or wood lamp examination.[1,2]

In a review of the clinical features of 159 patients with Legius syndrome (LS), anemic nevi were not reported[4]; however, they can easily be overlooked if not specifically searched for. We report 2 patients with nonNF1 RASopathies and anemic nevi.

Abbreviations used:

α1-AR:	α1-adrenergic receptors
CALMs:	café au lait macules
MAPK:	mitogen-activated protein kinase
NF1:	neurofibromatosis type 1
RAF1:	rapidly accelerated fibrosarcoma-1
RAS:	rat sarcoma family of protooncogenes
PTPN11:	protein tyrosine phosphatase nonreceptor type 11
SPRED1:	sprouty-related, EVH1 domain containing protein 1

CASE REPORT

Patient 1, a 2-year-old girl with an infantile hemangioma, had >10 CALMs on the trunk and limbs but no other features of NF1. On her lower back, a nevus anemicus was present (Fig 1). Molecular genetic testing detected a *SPRED1* c.423+5G>C mutation, causing exon-4 skipping and confirming LS.

Patient 2, an adult man, had multiple CALMs, axillary and abdominal lentigines, and facial features resembling Noonan syndrome but no other signs of NF1. In addition, he had a nevus anemicus on the thorax. Molecular genetic testing showed a c.1492C>T (p.Arg498Trp) missense mutation in the *PTPN11* gene, which led to the diagnosis of Noonan syndrome with multiple lentigines.

These cases suggest that anemic nevi might rather be characteristic of the broader group of RASopathies in general. Because LS is rare (1/75,000) and Noonan syndrome with multiple lentigines even more rare, coincidental association with anemic nevi is unlikely.

DISCUSSION

The role of the RASpathway seems important in the pathogenesis of vascular malformations such as capillary malformation—arteriovenous malformation

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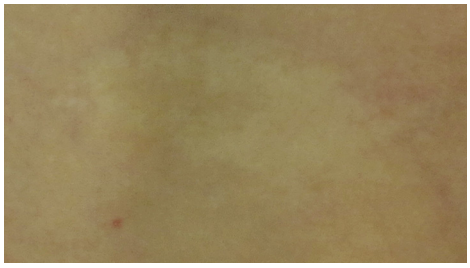

Fig 1. Typical nevus anemicus on trunk with sharp, irregular margins surrounded by smaller satellite macules. The picture is taken after rubbing and shows the absence of erythema in the patch.

syndrome, in which loss-of-function mutations in *RASA1* as well as in *EPHB4* have been identified.[5,6] Sturge-Weber syndrome has been linked to activating *GNAQ* mutations.[7] Moreover the study by Messiaen and colleagues and the study by Spurlock and colleagues showed LS patients with vascular anomalies.[8,9] Vascular and cerebrovascular defects have been associated with NF1 for a long time.[10] The exact pathogenesis of anemic nevi is not known, but they seem more common in NF1 and as our cases suggest in RASopathies in general.

Anemic nevi are hypothesized to result from vasoconstriction induced by localized hypersensitivity of cutaneous arteriolar α1-adrenergic receptors (AR) to catecholamines.[2,3,11] Because RAS-MAPK (rat sarcoma protooncogene family mitogen-activated protein kinase) activation results from α1-AR activation and RAS itself is negatively regulated by neurofibromin, local absence of neurofibromin in smooth muscles of the skin arterioles could potentiate the effect of α1-AR–mediated vasoconstriction resulting in anemic nevi.[1-3]

However, this pathway is also overactive in other RASopathies, and if this hypothesis is true, anemic nevi should also be more frequent in those patients. Another hypothesis, more specific to NF1, suggests that non–RAS-related properties of neurofibromin, such as the regulation of G-protein–coupled adenylate cyclase, might interfere with α1-AR.[3] Finally, in cultured fibroblasts from NF1 patients, loss of β-AR has been shown to induce increased α-adrenergic stimulation.[12] In arterioles, this might cause anemic nevi. All these hypotheses remain to be proven.

More patients with RASopathies need to be investigated clinically for anemic nevi. We advise confirmation of the diagnosis of NF1 in children with CALMs and a nevus anemicus by molecular genetic testing. If frequent occurrence of anemic nevi in the group of RASopathies is confirmed, then they should not be used as an independent criterion for NF1.

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