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CASE REPORT

Giant congenital melanocytic naevus caused by *NRAS* Q61K mosaicism

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Abstract

Giant congenital melanocytic naevi (CMN) are large melanocytic lesions commonly associated with neurologic abnormalities. Patients diagnosed with giant melanocytic naevi are at an increased risk of developing melanoma compared to patients with smaller congenital naevi. If patients develop central nervous system (CNS) lesions and exhibit certain characteristic facial features, then the diagnosis of CMN syndrome can be made. We here present the case of a 24-year-old female who presented with multiple melanocytic naevi, which had been apparent since birth, and was diagnosed with giant melanocytic naevi caused by *NRAS* Q61K mosaicism. Both close follow-up of imaging and clinical study is important so as not to miss cutaneous malignancy and CNS lesions.

KEYWORDS
giant melanocytic naevus, melanoma, *NRAS*

INTRODUCTION

Giant melanocytic naevi (congenital melanocytic naevi [CMN], OMIM #137550) are large melanocytic lesions that may cover up to 80% of the body surface area and are commonly associated with neurological abnormalities.[1] Small CMN are present in about 1% of neonates, whereas giant CMN are much rarer. In about 20% of children with giant CMN, foci of melanin-producing cells within the brain parenchyma are present, which may develop into neurocutaneous melanosis.[1–3] Other neurologic findings include hydrocephalus, arachnoid cysts, syringomyelia, and tumours.[4] Neurologic symptoms may be present in patients without radiologic signs of disease. Not only that neurological abnormalities may impact the clinical course of patients, but there is also an increased risk for the development of melanoma. The likelihood of developing melanoma increases with the size of lesions of CMN to about 10%–15%, thus causing a lifetime risk in those with the largest naevi, although this high number

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may be due to a selection bias of smaller studies.[5,6] CMN arise from postzygotic mutations, most frequently altering the Q61 codon of the *NRAS* gene (OMIM *164790).[7] Mosaicism is usually present in lesional tissue specimens, but it is not present in blood samples or specimens of unaffected skin. We here report the case of a 24-year-old woman who had multiple melanocytic naevi since birth and was diagnosed with giant melanocytic naevi caused by a postzygotic mutation in codon Q61 in the *NRAS* gene.

CASE REPORT

A 24-year-old woman who presented to our outpatient clinic in June 2018 had multiple melanocytic naevi, which had been apparent since birth (Figure 1). She had been treated with dermabrasion and laser therapy at an early age, which resulted in some areas being less pigmented, but since then multiple new lesions have arisen. We performed biopsies from melanocytic lesions to obtain an adequate diagnosis, rule out the possibility of melanoma and perform molecular genetic diagnostics. Histology revealed papillomatous epithelium with enlarged rete ridges and aggregates of melanocytes without any signs of atypia extending into the subcutaneous tissue (Figure 2). Magnetic resonance imaging (MRI) of the head was performed and no signs of leptomeningeal involvement or other abnormalities were observed. Genetic consultation revealed no family history of genetic disorders. Targeted next-generation sequencing of a panel of 42 genes known or suspected to be involved in mosaic disorders was performed on DNA extracted from two formalin-fixed, paraffin-embedded tissue biopsy samples, using a TruSeq Custom Amplicon Low Input Library Prep Kit (Illumina) for the enrichment and a MiSeq system (Illumina) for sequencing with an average coverage of the target region of >2000×. A known pathogenic variant, c.181C > A (Q61K), was detected in the two lesional tissue samples with an alternate allele frequency of 37% (2559 of 6743 reads and 3267 of 8743 reads, respectively). Other pathogenic

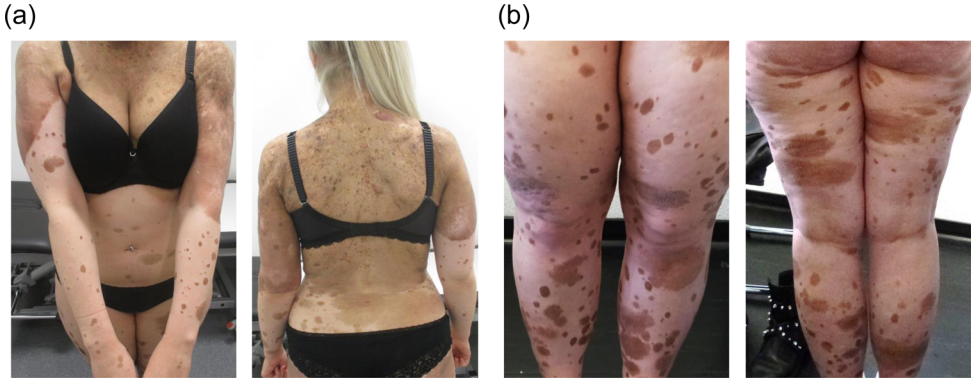

FIGURE 1 Clinical features of giant congenital melanocytic naevus (CMN). Clinical features of giant CMN. Multiple melanocytic lesions are visible on the trunk (a), as well as on the legs (b).

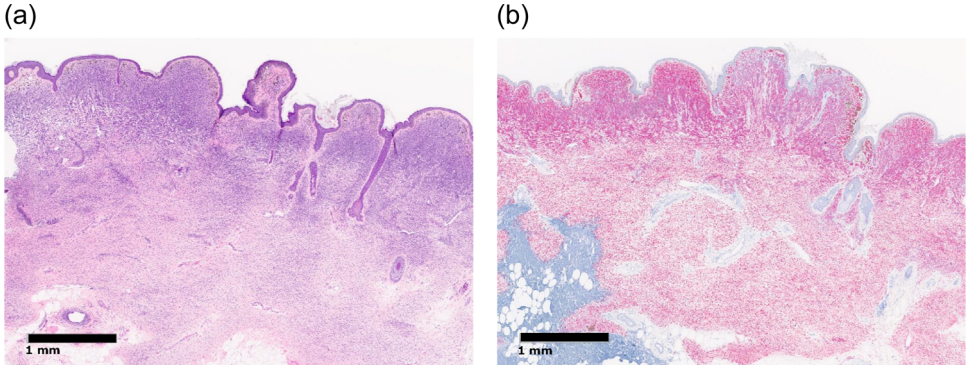

FIGURE 2 Histopathological findings. Histological presentation of the tumour (haematoxylin–eosin stain; scale bar = 1 mm) (a). Naevus cells extend into the septa of the subcutaneous adipose tissue. Histological presentation of the tumour (Melan A immunohistochemistry; scale bar= 1 mm) (b).

variants were not detected. In DNA samples from a buccal swab specimen and blood leucocytes, the *NRAS* mutation was not detected. Therefore, the diagnosis of a giant melanocytic naevus caused by a postzygotic *NRAS* mutation was made. Close clinical follow-up every 3 months with intermittent cranial MRI has not revealed any signs of malignancy to date.

DISCUSSION

Giant CMN result from an abnormal development in melanocytic progenitor cells, which may develop into melanoma of the skin or CNS lesions. Kinsler et al.[8] have proposed diagnostic criteria, consisting of (1) CMN of greater than 5 cm and (2) neurologic involvement (clinically or radiologic) and/or 3 or more typical facial features, such as prominent forehead, periorbital fullness, small short nose with narrow nasal ridge, round face, full cheeks, prominent premaxilla and everted lower lip. Postzygotic *NRAS* mutations are present in a majority of the cases, with Q61K and Q61R being the most common amino acid changes.[7,9] Consistent with previous reports, *NRAS* mutations were absent from unaffected tissue and blood samples in our presented case. To detect potential other mutations present within the tissue specimens, which might have an impact on the patient's clinical course, a 42-gene targeted next-generation sequencing panel was performed, which did not show other mutations. *BRAF* mutations are also reported in a subgroup of CMN patients. They are reported only sporadically in giant CMN, while they are more prevalent in small CMN.[7]

Neurological symptoms and CNS abnormalities in MRI are well-known complications in CMN and the incidence rises with the projected size of adult naevi. About 40% of patients with naevi larger than 40 cm in size develop either neurological symptoms or exhibit abnormal MRI findings. CNS involvement may require neurosurgical intervention.[5]

Therapeutic options remain limited; while dermabrasion, surgical intervention and laser interventions have been described, they all exhibit disadvantages. Although surgical intervention is often not a viable option for patients with anything but small CMN, laser treatment and dermabrasion appear more viable options. However, both exhibit a high rate of recurrence in patients undergoing dermabrasion and laser interventions, as it was seen in the presented case.

This case report demonstrates a typical clinical presentation of giant melanocytic naevus in a 24-year-old patient who has an increased risk of developing melanoma or neurological symptoms. Although the patient does not fulfil all diagnostic criteria of congenital melanocytic naevus syndrome, we proposed a close clinical follow-up as the patient showed extensive cutaneous involvement with numerous "satellite naevi." We scheduled routine clinical follow-up every 3 months and will consider further cranial MRI to rule out leptomeningeal involvement.

AUTHOR CONTRIBUTIONS

Carl M. Thielmann, Eva Hadaschik, Antje Kampmeier and Alma Küchler analysed and interpreted patient data. Carl M. Thielmann, Klaus Griewank and Eva Hadaschik were major contributors in writing the manuscript. Martin Zenker and Ilse Wieland performed molecular analysis. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

Frederik Krefting declares personal fees from Novartis. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

We thank the patients in this study who have given written informed consent to the publication of their case details.

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