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Diagnosis of Mosaic RASopathy in a Child with Rhabdomyosarcoma

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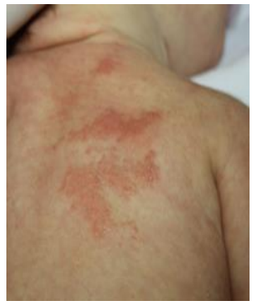
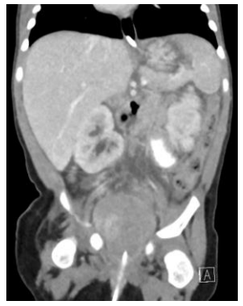
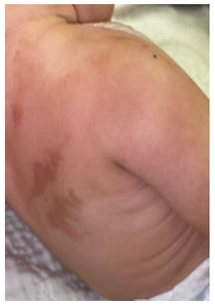
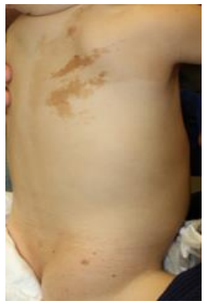
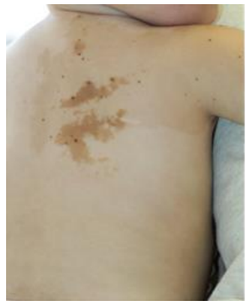
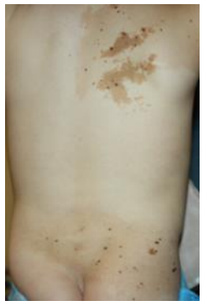
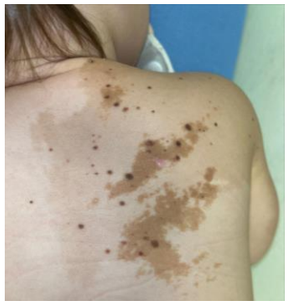
Background

- Phacomatosis pigmentokeratotica (PPK) is a rare subtype of epidermal nevus syndrome characterized by the co-existence of a sebaceous nevus and speckled lentiginous nevus described in ~30 cases in literature.
- PPK is now recognized as a mosaic RASopathy due to a post-zygotic mutation in the Ras-Raf-MEK-ERK pathway.
- RAS variants are also known to contribute to tumorigenesis in some pediatric cancers, including rhabdomyosarcoma.

Patient Presentation

- The patient is a former 32-week premature female who presented to dermatology clinic at 2 months of age for evaluation of skin-colored to pink linear plaques on her right back and shoulder and a brown macule on her right arm.
- She was diagnosed with a congenital melanocytic nevus and epidermal nevus with the possibility of having an epidermal nevi syndrome.
- At 4 months of age, she was hospitalized for obstructive renal failure secondary to a pelvic mass.
- Biopsy of the mass was diagnostic for fusion negative rhabdomyosarcoma. Genetic testing of the tumor revealed a copy-neutral loss of heterozygosity of 11p15.5 and a *HRAS* G13R pathogenic mutation.
- Germline testing for Beckwith-Wiedemann Syndrome and *HRAS* were negative, which began the journey of finding a unifying diagnosis between her skin findings and cancer diagnosis.

Clinical Course

Nov 2021
Diagnosed with congenital melanocytic nevus and epidermal nevus with possibility of epidermal nevus syndrome

Jan 2022
Diagnosed with fusion negative rhabdomyosarcoma with a *HRAS* G13R mutation; germline *HRAS* testing was negative

June 2022
Underwent tumor resection and epidermal nevus biopsy at Mayo Clinic; WES on the biopsy sample showed a VUS in *PORCN* – determined to be non-contributory

July – Dec 2022
Patient had ongoing evolution of cutaneous findings including the thickening of plaques involving the back, neck, chest, right arm and a tan patch on the right lower back

Jan 2023
Re-evaluation by dermatology; Patient was found to have papular nevus spilus and epidermal nevus with cutaneous findings of tan patches with several brown macules and papules admixed with tan linear plaques in blaschkoid distribution concerning for PPK. She was also noted to have hemihypertrophy of her left leg

May/June 2023
Seen in Derm/Genetics/Neuro clinic due to PPK concern

SNP-based microarray on blood was negative for germline CNVs

Sept 2023
Underwent biopsies of an epidermal nevus and a nevus spilus– both showed *HRAS* G13R mutation

Confirmation of PPK diagnosis

Genetic testing performed throughout patient's clinical course

Test	Results
Cancer Microarray on tumor sample	• Gain of chromosome 2, 3, 5, 8, and 11 • Copy-neutral loss of heterozygosity (CN-LOH) of 11p15.5
FISH analysis on tumor sample	• *FOXO1* fusion negative
Beckwith-Wiedemann Syndrome testing on blood	• Negative – normal methylation pattern and copy number of ICI1 and ICI2
Next Generation Sequencing (NGS) multi-gene panel on blood	• Negative for sequence or copy number variants (CNVs) in *CDKN1C, DICER1, HRAS, NF1, TP53*
FoundationOne® Heme (comprehensive genomic profiling) on tumor sample	• ***HRAS* G13R pathogenic mutation**
Comprehensive NGS Panel on blood	• Negative for reportable variants
Whole exome sequencing (WES) on epidermal nevus biopsy sample	• Variant of uncertain significance (VUS) in *PORCN*
Single nucleotide polymorphism (SNP)-based microarray on blood	• Negative for germline CNVs
WashU's PIK3CA-Related Overgrowth Spectrum Disorders Panel: Comprehensive Panel via NGS on 2 skin biopsy samples	• Sample 1 – ***HRAS* G13R pathogenic mutation**, VUS in *PIEZO1* • Sample 2 – ***HRAS* G13R pathogenic mutation**, VUS in *HRAS* and *PIEZO1*

Conclusions

- Mosaic RASopathies remain a diagnostic challenge as tissue involvement can be varied and evolve over time, DNA sequencing of the blood is often negative, and phenotypes can depart from germline RASopathies.
- With only case reports and small case series describing an association between cutaneous mosaic RASopathies and rhabdomyosarcoma, there is a need for further awareness of this association as it may impact treatment decisions and necessitate multidisciplinary care.
- Unfortunately, the risk of malignancies for patients with mosaic RASopathies is unknown and therefore cancer screening guidelines are not well established for this patient population.

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