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CASE REPORT **Open Access**

Epigenomic characterization and therapeutic challenges of melanoma arising in giant nevi in pediatric patients

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Abstract

Background Congenital giant melanocytic nevi (CGMN) are rare melanocytic proliferations present at birth, associated with an increased risk of pediatric malignant melanoma (MM). Melanomas arising within CGMN are uncommon but clinically aggressive, with diagnostic challenges due to overlapping histopathological features with benign proliferations. This case series explores the clinicopathologic, molecular, and therapeutic profiles of three pediatric patients with MM arising in CGMN.

Methods An integrated analysis—including histopathology, immunohistochemistry, mutational profiling (*NRAS*, *BRAF*, *PRKAR1A*), copy number variation (CNV) analysis, and DNA methylation profiling using the classifier developed at the German Cancer Research Center (DFKZ) in Heidelberg—was performed on tumor and matched nevus samples.

Results All tumors harbored MAPK pathway alterations, including *NRAS Q61* mutations or *BRAF* fusions. DNA methylation profiling confirmed malignant transformation, while matched nevi clustered as melanocytoma with flat CNV profiles. Immunotherapy with checkpoint inhibitors (nivolumab ± ipilimumab) was used in all cases despite low PD-1/PD-L1 expression. However, therapeutic response was inconsistent, and two patients developed severe immune-related hepatitis requiring treatment discontinuation. Only one patient remains in remission. Epigenomic analyses revealed that benign and malignant components shared a close clustering pattern, suggesting a common cellular origin and patient-specific epigenetic imprinting.

Conclusion MM arising within CGMN poses diagnostic and therapeutic challenges. While molecular and epigenomic profiling supports accurate classification and understanding of disease biology, the role of immunotherapy remains uncertain—marked by reduced efficacy and significant immune-related toxicity. A multidisciplinary approach is essential to guide management and improve outcomes in this rare pediatric malignancy.

Keywords Case report, Congenital giant melanocytic nevus, Pediatric melanoma, *NRAS* mutation, DNA methylation profiling, Immune checkpoint inhibitors, *BRAF* fusion, CNV

1 Introduction

Congenital giant melanocytic nevi (CGMN) are rare melanocytic proliferations present at birth, defined by their large size—typically exceeding 20 cm in projected adult diameter—and their potential to cover significant portions of the body surface [1] The estimated incidence of CGMN ranges from 1 in 20,000 to 1 in 50,000 live births, depending on the diagnostic criteria and population studied [2, 3]. While the majority of CGMNs remain benign, they are associated with an increased lifetime risk of malignant transformation, primarily into melanoma. This risk is particularly elevated during early childhood, with most transformations occurring before the age of 10 [4, 5].

Pediatric malignant melanoma (MM) arising within CGMN is exceedingly rare and often present with distinct clinical and biological features compared to adult melanoma. These tumors tend to exhibit aggressive behavior, with early local invasion and a higher likelihood of central nervous system involvement, particularly in cases associated with neurocutaneous melanosis [2]. Histopathological diagnosis can be challenging, as features overlap with proliferative nodules and atypical melanocytic proliferations seen in CGMN, necessitating the integration of molecular and genetic analyses for accurate classification.

Molecular studies have implicated aberrant activation of the MAPK pathway as a driver event in both CGMN and associated melanomas, with frequent *NRAS Q61K/R* mutations and, less commonly, *BRAF V600E* alterations [6, 7]. These mutations may contribute to oncogenic transformation in a subset of lesions, underscoring the relevance of molecular profiling for both diagnostic clarity and therapeutic decision-making. Recent advances in targeted therapies and immunotherapies—such as MEK inhibitors for *NRAS*-mutant tumors and immune checkpoint inhibitors (anti-PD-1/PD-L1, anti-CTLA-4)—have expanded treatment options for melanoma. However, their application in pediatric patients remains off-label and is supported by limited clinical data [8].

In this case series, we present three pediatric patients with melanoma arising in congenital giant melanocytic nevi (CGMN), highlighting their clinical features, genomic and epigenomic profiles, and treatment courses. Special attention is given to their responses and adverse events associated with systemic therapies, particularly immune checkpoint inhibitors and targeted agents. These findings add to the limited body of knowledge on this rare condition and emphasize the value of a multidisciplinary approach—integrating clinical, histopathological, and molecular insights—to inform diagnosis, therapeutic decision-making, and management of treatment-related toxicity.

2 Case #1

A 3-month-old girl was diagnosed with MM of the cervical region arising within a CGMN. Initial staging showed no evidence of nodal or distant metastases. Molecular analysis via PCR and direct sequencing identified a pathogenic *NRAS* (OMIM*164790) variant at codon 61 (c.181 C > A, p.Gln61Lys NM_002524.5). No mutations were detected in exons 2, 4, or 5 of *NRAS*. The tumor tested negative for *BRAF* mutations and *TERT* promoter mutations. At nearly four years of age, she underwent surgical excision of a suspicious nodule in the right interscapular region, within the giant nevus and lower to the initial MM site. Histopathological examination revealed a predominantly dermal proliferation with minimal extension into the subcutaneous tissue. The neoplastic cells exhibited an epithelioid morphology, characterized by dispersed chromatin and prominent nucleoli. The mitotic index was 8–9 mitoses per 10 high-power fields (HPF), with occasional atypical mitotic figures identified. No evidence of angioinvasion was observed. The lesion extended close to one of the radial margins, with a minimum clearance of 0.3 mm, and a minimum deep margin distance of 0.7 mm. The proliferative index, assessed by Ki-67 immunostaining, was approximately 15%. A subsequent wide local excision showed no residual melanoma at the margins; however, a separate 5-mm nodular proliferation was identified and was completely excised. A sentinel lymph node biopsy was not performed. PET-CT scans showed no residual or metastatic disease. Further immunohistochemical analysis demonstrated a nuanced expression pattern: PD-1 was undetectable on neoplastic cells, yet present in a few isolated elements within the sparse inflammatory infiltration. PD-L1 was observed in approximately 2% of tumor cells but was absent in the limited inflammatory component (Fig. 1a, upper panels). Despite this low expression profile, the decision was made to begin adjuvant immunotherapy with nivolumab at 3 mg/kg every two weeks. After five months, a new occipital nodular lesion adjacent to the previous ones was surgically removed and confirmed as MM. Nivolumab was continued. Four months later, recurrence in the left axillary lymph nodes was noted. Surgical excision revealed metastatic MM with positive surgical margins, and combined immunotherapy with ipilimumab 3 mg/kg and nivolumab 1 mg/kg every 3 weeks was started. After the fourth dose of combination therapy, the patient developed hepatotoxicity characterized by an elevation of transaminases exceeding 30 times the upper limit of normal. Treatment was discontinued, and high-dose corticosteroids were initiated. However, due to the lack of response in controlling hepatic cytolysis and a progressive increase in cholestasis, mycophenolate mofetil was added. This led to a gradual decline in liver cytolysis markers and allowed for progressive tapering and eventual discontinuation of corticosteroids after two months of treatment. Mycophenolate mofetil was maintained for an additional month and then discontinued. During the period of immunotherapy discontinuation, the patient experienced disease progression with metastases in axillary lymph nodes and in the lung (Fig. 1b). She was switched to trametinib and vemurafenib, but progressive disease was documented after three months. The patient died 20 months after the diagnosis of her third MM.

DNA methylation profiling [9] in the second malignant nodule showed a score of 0.73 for the methylation class (MC) Melanoma metastasis based on the Heidelberg Brain Tumor Classifier v12.5, consistent with the diagnosis of malignant melanoma. Accordingly, copy number variation (CNV) analysis revealed a complex genomic profile, including gains of chromosomes 1q, 6, 8q, 12, 15, 19, 20, and 21, along with a loss of 7q (Fig. 2a). In contrast, multiple samples from the CGMN (A2 and A3) were classified as melanocytoma with a score of 0.75 using the Heidelberg classifier, with an overall flat genomic profile by CNV analysis (Fig. 2b). Minor alterations were observed in sample A3, specifically telomere deletions on chromosomes 5p, 7p, 7q, and 10q (Fig. 2c), which are not uncommon in benign melanocytic proliferations.

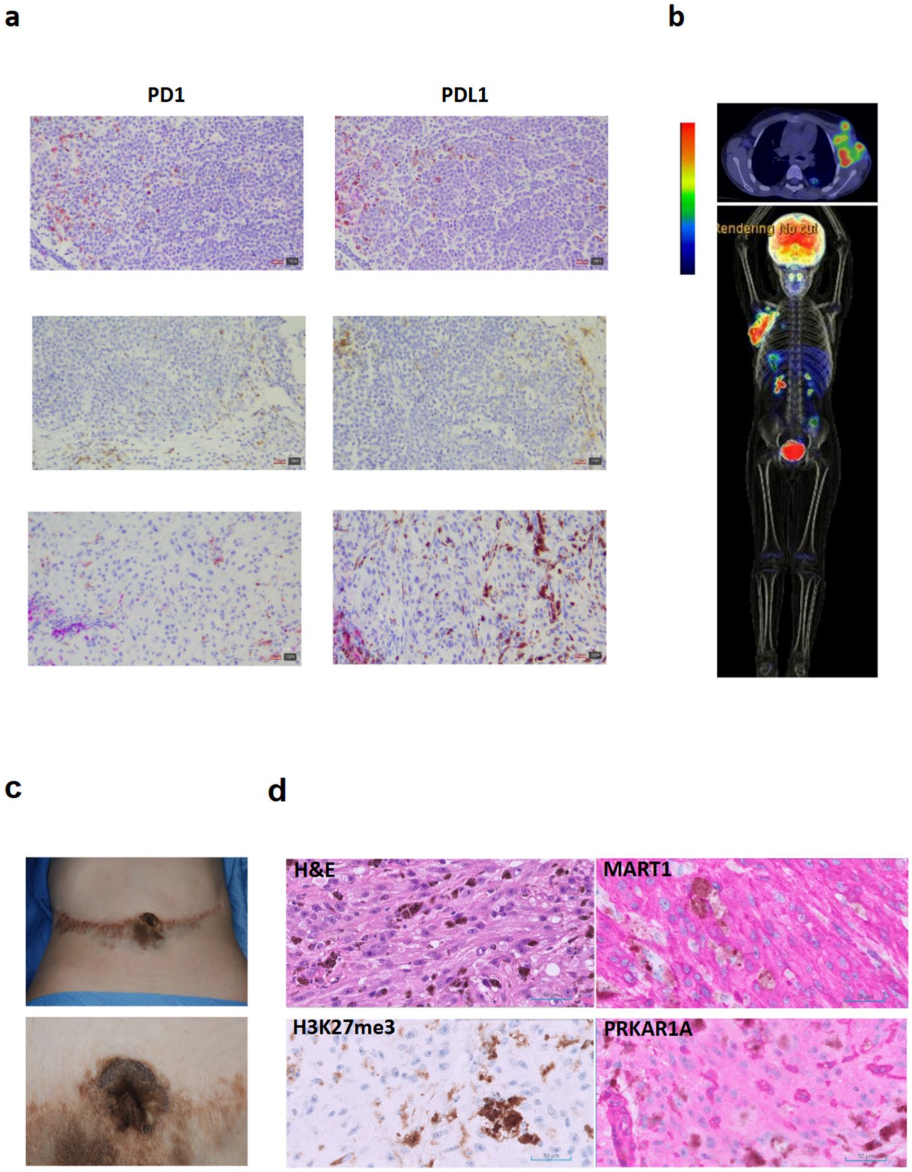


Fig. 1 Clinical and pathological features of the three cases. **a –** PD1 and PDL1 staining of case #1 (upper panels), case#2 (middle panels) and case #3 (lower panels) **b –**Positron emission tomography (PET) scans of Case #1 showing axillary lymph nodes and pulmonary metastases. The upper panel presents axial images, while the lower panel displays a full-body coronal view. The scale bar represents capitation intensity, with color intensity ranging from blue (low uptake) to red (high uptake). **c –** Left: Case #3, A 12-year-old girl with a giant pigmented cutaneous lesion occupying the right side of the abdomen and extending slightly beyond the linea alba to the left. The lesion underwent multiple excisions and is characterized by a blackish hue with intermixed hyperpigmented areas and irregular, poorly defined borders. A dark nodule with irregular and poorly defined borders is observed in the umbilical region within the residual CGMN (detail in the lower panel). **d –** Histopathological evaluation of the metastatic lymph node from case #3: Hematoxylin and eosin staining (top left) shows an epithelioid cell neoplasm with eosinophilic nucleoli and large cytoplasms sometimes containing brownish granules. Immunohistochemical stainings show diffuse positivity for MART1 (top right) and loss of nuclear expression of H3K27me3 (bottom left) and PRKAR1A (bottom right)

3 Case #2

A female infant born with a CGMN involving the trunk, left hand, and scalp underwent excision of a right inguinal lesion at three years of age. The lesion was located within an area of congenital melanocytic nevus and comprised two well-circumscribed

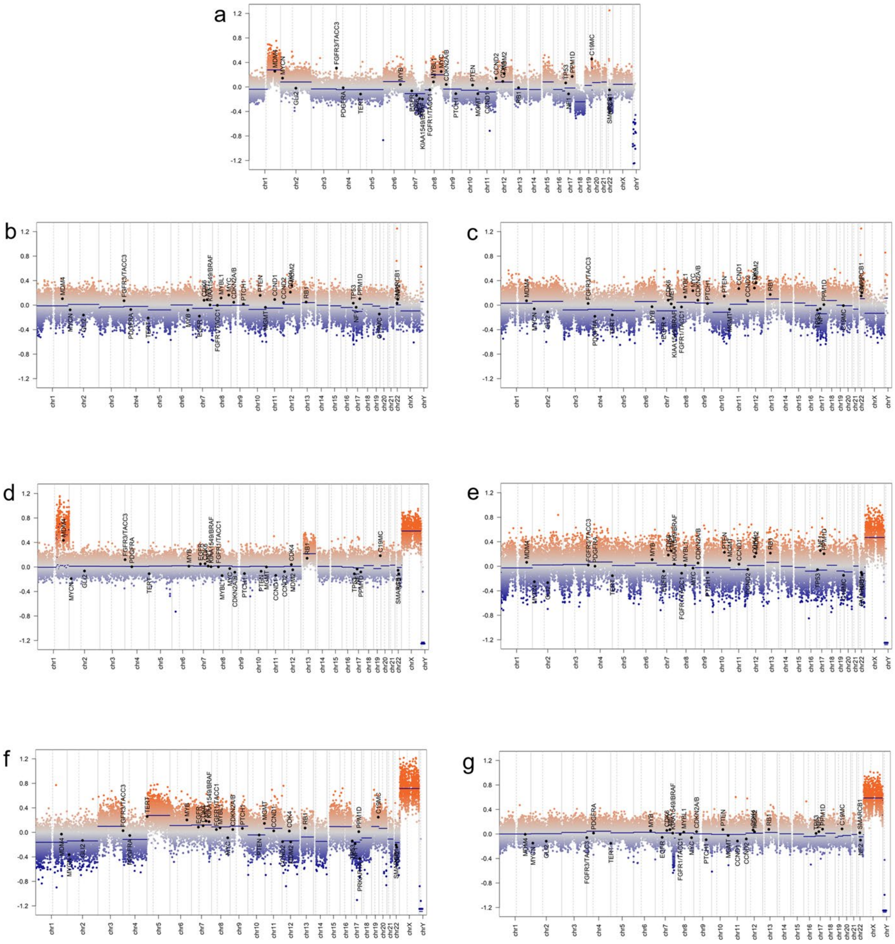


Fig. 2 CNV plots generated from DNA methylation data of each study sample. **a** – Melanoma sample from patient 1; **b** – Nevus from case #1 (sample A2); **c** – Nevus from case #1(sample A3); **d** – Melanoma sample from case #2; **e** – Nevus sample from case #2; **f** – Melanoma sample from case #3; **g** – Nevus sample from case #3. CNV analysis was performed via the conumee Bioconductor package as previously described [13]

nodules involving both the dermis and subcutaneous tissue. Histopathologically, these nodules were composed of cells with vaguely epithelioid morphology, characterized by leptochromatic nuclei and prominent nucleoli. The mitotic index was elevated, with 20 mitoses per 10 high-power fields (HPF), including focal atypical figures. Osteoid-like hyalinization was observed within the nodular proliferation. No evidence of angioinvasion was identified. Immunohistochemical staining revealed diffuse expression of MART-1 in both the nodules and the nevus component. HMB45 was diffusely positive in the nodules and focally expressed in the superficial portion of the congenital nevus. Notably, the expression of H3K27me3 was lost in the nodular component but retained in the underlying congenital nevus. Molecular profiling via CGH-array, performed separately on the nodules and the congenital nevus, revealed trisomy of chromosomes 8 and 13, along with multiple segmental amplifications involving the entire long arm of chromosome 1 (1q) in the nodules. The nevus component displayed a balanced genomic profile. Both the *BRAF* hotspot regions and the *TERT* promoter were wild-type, while revealed a pathogenic *NRAS* variant (c.182 A > G, p.Q61R), detected both in the MM and in the nevus. Overall, the combination of morphological features—such as severe atypia and high mitotic index—along with segmental chromosomal aberrations on 1q and loss of H3K27me3 expression, supported the interpretation of malignant transformation arising within a congenital nevus. Further **i**mmunohistochemical analysis showed PD1 negativity in tumor cells, but 10% positivity in the inflammatory infiltrate. PDL1 expression was 3% in tumor cells and negative in the surrounding lympho-histiocytic infiltrate (Fig. 1a middle panels). The patient underwent wide local excision and sentinel lymph node biopsy, which demonstrated nodal involvement. Adjuvant immunotherapy with ipilimumab and nivolumab was started. Despite treatment, a local relapse occurred within six months. She was treated sequentially with temozolomide and vemurafenib, but neither therapy yielded clinical benefit. The disease progressed rapidly, and she died 24 months after initial MM diagnosis.

By DNA methylation analysis, the MM component classified as MC Melanoma metastasis (score 0.30), with gains in chromosome 1q and 13 (Fig. 2d). On the other hand, the CGMN was classified as MC melanocytoma (score 0.36) and revealed a flat genomic profile (Fig. 2e).

4 Case #3

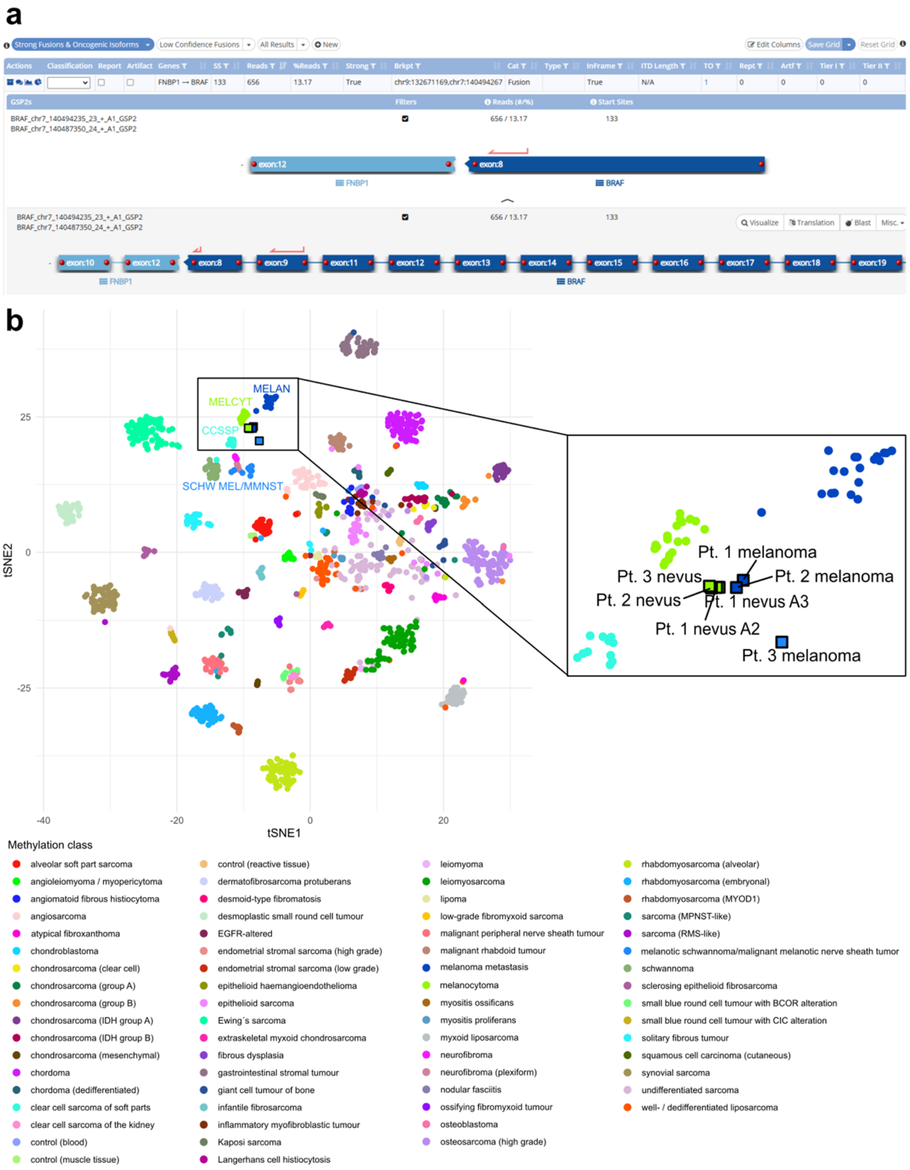
A 12-year-old girl with a CGMN of the abdomen had undergone multiple partial excisions since the age of two, using tissue expansion techniques (Fig. 1c). During a routine plastic surgery evaluation, a large right inguinal lymphadenopathy was identified. Brain CT and PET-CT scans were negative. The remaining portion of the CGMN and the lymph-node were surgically removed. The CGMN was free of melanoma, while the lymph node harbored a lesion composed of spindle-shaped cells with prominent nucleoli and eosinophilic cytoplasm, occasionally containing marked pigmentation. Mitotic rate was low (1–3 mitoses/mm^2). Numerous clusters of melanophages were also observed. Immunohistochemically, the neoplastic cells showed positive staining for MART-1, HMB45, and S100. The expression of p16, PRKAR1A and H3K27me3 was decreased; BAP1 was largely retained and Beta-catenin exhibited cytoplasmic staining; PRAME was negative **(**Fig. 1d**)**. Neoplastic cells were negative for PD1 and PDL1 with scattered positive small lymphocytes. (Fig. 1a lower panels).

Molecular analysis by DNA NGS revealed a heterozygous deletion of the gene *PRKAR1A* on chromosome 17, which supported the immunohistochemical loss of expression of PRKAR1A (TruSightTM Oncology 500 [10]). In addition, an *FNBP1*::*BRAF* fusion was identified by a Custom RNA Fusion Gene Panel (ArcherDX) (Fig. 3a).

By DNA methylation profiling, the nodal lesion classified as "MC malignant melanotic nerve sheath tumor (MMNST)" (Score 0.89) and showed a highly complex CNV profile (Fig. 2f), while the nevus portion classified as MC melanocytoma (score 0.95), with a flat CNV profile and a *BRAF* gene alteration (Fig. 2g).

The t-SNE analysis, performed by using selected DFKZ reference classes [9, 11], showed that nevus and lymph node lesion clustered in close proximity and were distant from de novo melanomas (Fig. 3b), in keeping with a shared cellular origin, besides the strong patient-specific influences.

Taken together these findings suggest that the lymph node lesion is consistent with a PRKAR1A-inactivated melanoma (PEM-like melanoma) [12]. The attribution to the malignant melanotic nerve sheath tumor" class of the Heidelberg classifier might be related to the common molecular alteration in PRKAR1A in both neoplasms. However, the histogenetic relationship of lymph node lesion with the congenital nevus, supported



Actions	Classification	Report	Artifact	Genes	SS	Reads	%Reads	Strong	Brkpt	Cat	Type	InFrame	ITD Length	TO	Rept	Artf	Tier I	Tier II
		☐	☐	FNBP1 → BRAF	133	656	13.17	True	chr9:132671169,chr7:140494267	Fusion		True	N/A	1	0	0	0	0

GSP2s	Filters	Reads (#/%)	Start Sites
BRAF_chr7_140494235_23_+_A1_GSP2 BRAF_chr7_140487350_24_+_A1_GSP2	☑	656 / 13.17	133
BRAF_chr7_140494235_23_+_A1_GSP2 BRAF_chr7_140487350_24_+_A1_GSP2	☑	656 / 13.17	133

Fig. 3 Molecular findings **a -** Representation of structural rearrangements between chromosomes 9 and 7, showing the in-frame *FNBP1::BRAF* fusion in both the background GCM and melanoma in case #3; NGS library was carried out using Archer Custom Fusion Plex Kit (Invitae, San Francisco, CA) according to the manufacturer's protocols and sequencing run was performed in paired-end mode (2 × 151-bp reads) using the Illumina MiSeQ platform **b** – t-SNE analysis of DNA methylation data. After raw data loading, filtering and normalization, 10,000 probes with highest standard deviation were used to compute the 1-variance weighted Pearson correlation between the samples, and its corresponding distance matrix was used as input of Rtsne function from Rtsne package (https://CRAN.R-project.org/package=Rtsne). Dot color represents each sample's methylation class assigned by the Heidelberg Brain Tumor Classifier v12.5 or the sarcoma classifier. The reference cohort, represented by round dots, contains entities from Koelsche et al. (1494 samples) and Capper et al. (58 samples); together with 15 EGFR-altered samples (12 from Vallese et al., 3 unpublished). The study samples are represented by black-bordered squares. The methylation clusters closest to the study samples are "melanoma metastasis" (MELAN, blue); "melanocytoma" (MELCYT, green); "clear cell sarcoma of soft parts" (CCSP, aqua), and melanotic schwannoma/malignant melanotic nerve sheath tumor (SCHW MEL/MMNST, light blue). The panel on the right zooms in on the main samples cluster

by the close relationship at methylation profiling, together with the *BRAF* alterations, are strong evidence in support of PRKAR1A-inactivated melanoma. In this context, the difference in CNVs reflects the additional alterations acquired in the malignant transformation.

After the integrated diagnosis, the patient was treated with combined ipilimumab and nivolumab, but at the end of the second dose, she developed immune-mediated hepatitis, requiring corticosteroids and therapy was discontinued. Upon resolution, she resumed treatment with nivolumab monotherapy. The patient remains in complete remission and continues treatment with nivolumab.

5 Discussion

Malignant melanoma (MM) arising in congenital giant melanocytic nevi (CGMN) represents a rare but particularly aggressive subset of pediatric melanoma. In this series, two of three patients (case #1 and case #2) developed MM during infancy and experienced rapid disease progression despite prompt diagnosis and intensive multimodal treatment. Both tumors harbored activating *NRAS* mutations at codon 61, a well-characterized oncogenic driver in CGMN-associated melanoma, known to activate the MAPK signaling pathway [6].

The third patient (case #3) was a diagnostic challenge for two reasons: lack of a malignant component in the congenital nevus and the peculiar morphologic, molecular and epigenetic features. Although the *FNBP1::BRAF* fusion identified by NGS is rare, *BRAF* rearrangements have been reported in GCMN [14]. However, the assignment of the lymph node lesion, to the "malignant melanotic nerve sheath tumor" methylation class, emphasizes the need of integration of the methylation and molecular data in the appropriate context.

In fact, PRKAR1A inactivation is not exclusive to MMNST but is also characteristic of PEM-like melanomas, which have been reported to arise within congenital nevi. Thus, based also on the *BRAF* alteration detected in the lymph node lesion and in the GCMN it may be hypothesized that both are derived from a common cell of origin. In addition, the complex CNV profile in the lymph node localization reflects the malignant evolution.

The original training set for this class included only 8 melanotic schwannomas in version 11b4 of the Brain Tumor Classifier, with 4 additional cases in the validation set [9]. These same cases were carried forward into subsequent classifier versions, but detailed histopathological data are not available, and we cannot exclude the possibility that PEM-like melanomas were represented.

For these reasons, both MMNST and PEM-like melanoma remain valid differential diagnoses. This diagnostic uncertainty highlights the need for larger reference cohorts and integrated clinico-pathological and molecular analyses to improve the robustness of methylation classifiers for rare melanocytic neoplasms.

In addition to aiding classification, DNA methylation profiling provided valuable insight into CNV status. The data suggest that, from an epigenetic standpoint, these samples constitute entities that are distinct from conventional *de novo* melanomas. This supports the hypothesis that both the biological context and evolutionary trajectory of the tumor have a substantial impact on the epigenetic landscape. Within this framework, CNV analysis emerges as a particularly informative tool. While the epigenetic profiles alone may not clearly distinguish these samples from nevi, CNV alterations provide a more definitive diagnostic indication of malignancy. All MM cases exhibited highly aberrant CNV profiles, consistent with genomic instability, whereas the associated

CGMNs showed near-flat CNV landscapes—supporting their benign nature. These findings reinforce the utility of combining epigenomic and genomic profiling to distinguish benign proliferations from malignancies in the context of CGMN.

The molecular heterogeneity observed in these cases underscores the importance of comprehensive genomic profiling to guide potential therapeutic strategies. While the patients received immune checkpoint inhibitors (ICIs) and targeted agents, clinical responses were heterogeneous and generally transient.

Of note, the combination therapy in Cases #2 and #3 was administered on a compassionate-use basis, considering the high-risk stage III disease, limited pediatric data, and poor prognosis associated with *NRAS*-driven or aggressive melanoma subtypes. Indeed, this combination is not standard or approved in the adjuvant pediatric setting, and the treatment decisions were individualized by a multidisciplinary tumor board.

ICIs, including ipilimumab (a CTLA-4 inhibitor) and nivolumab, have transformed cancer treatment by enhancing the immune system's ability to recognize and attack tumor cells. These agents work by releasing the natural "brakes" on T-cell activity, thereby promoting a stronger and more sustained anti-tumor response. Despite low PD-1/PD-L1 levels, the substantial body of evidence indicates that initiating nivolumab (a PD-1 inhibitor) remains a scientifically justified and clinically sound approach in this context—aiming for durable responses beyond what PD-1 expression alone could predict. Indeed, this choice was grounded in robust clinical evidence in adult population demonstrating that PD-1 or PD-L1 negativity does not preclude a meaningful response to PD-1 inhibitors. In the pivotal CheckMate trials of nivolumab monotherapy versus dacarbazine, objective response rates (ORRs) reached 41.3% in PD-L1–negative tumors—albeit lower than the 57.5% ORR seen in PD-L1–positive melanomas [15]. Importantly, around one-fifth of patients with PD-1/PD-L1–negative melanoma still achieved significant clinical benefit. Additionally, long-term follow-up from CheckMate 067 supports the efficacy of combined nivolumab and ipilimumab even in PD-L1–negative tumors [16]. Further preclinical and case-based evidence suggests that other features—such as high tumor mutational burden and a robust CD8$^+$ T-cell infiltrate—may better predict response than PD-L1 status alone [17] and endorse PD-1 blockade in melanoma regardless of PD-L1 expression in the adult population. In one retrospective series, even patients with completely negative PD-L1 staining achieved complete remission on anti-PD-1 agents.

Notably, ICIs are associated with immune-related adverse events (irAEs) affecting multiple organ systems, including gastrointestinal, endocrine, hepatic, and dermatologic toxicities. In children, preliminary data suggest a spectrum of irAEs like adults, although long-term safety remains uncertain [20]. Combination therapies, such as CTLA-4 plus PD-1 inhibition, may increase both efficacy and risk of high-grade toxicities [21]. Management of significant irAEs typically involves systemic corticosteroids, with additional immunosuppressants used as needed.

Importantly, recent pediatric data from the MELCAYA study [18] further validate the role of anti–PD-1 therapy in children and adolescents with melanoma. This multicenter analysis showed encouraging response rates and a manageable safety profile, even in patients under 12 years of age. While most patients received PD-1 monotherapy, the study supports its use in both metastatic and adjuvant settings, reinforcing the rationale for its compassionate use in our series. In contrast to the MELCAYA study, which reported a relatively low incidence of irAEs in pediatric melanoma patients treated predominantly with anti–PD-1 monotherapy, our case series demonstrated a notably higher rate of toxicity. This discrepancy can be attributed to several factors: first, two of our patients received combination therapy with ipilimumab and nivolumab, a regimen known to significantly increase the risk of high-grade irAEs compared to PD-1 blockade alone. Second, the underlying biology of melanoma arising in congenital giant melanocytic nevi (CGMN)—including NRAS mutations and complex genomic alterations—may predispose heightened immune activation. Third, our patients were younger and treated in a compassionate-use setting for aggressive, high-risk disease, which may have necessitated more intensive immunotherapy. Finally, the small sample size and case-based nature of our report amplify the clinical impact of each adverse event, whereas MELCAYA's multicenter design and broader inclusion criteria likely diluted individual toxicity signals. These differences underscore the need for cautious interpretation and individualized risk-benefit assessment when applying immunotherapy in rare pediatric melanoma subtypes.

The rarity of MM arising in CGMN and the lack of prospective studies challenge the development of standardized treatment protocols. Nevertheless, accumulating evidence supports the concept that melanoma can arise in CMNs of any size, not exclusively in giant lesions. A recent systematic review [19] confirmed that although the relative risk is greatest for giant nevi, medium-sized and even small nevi may also undergo malignant transformation, as further illustrated by isolated case reports [20, 21]. This suggests that size alone should not be the sole criterion for surveillance intensity.

Effective clinical management of patients with CGMN demands a multidisciplinary approach. As emphasized by Kinsler et al. [5], early dermatological evaluation, longitudinal monitoring, and input from oncology, plastic surgery, and genetics teams are essential. The debate between early surgical excision and conservative management remains unresolved and must be individualized based on lesion characteristics, anatomical considerations, patient age, and family preferences.

Emerging data on the molecular and metabolic underpinnings of CGMN are beginning to shed light on the mechanisms of malignant transformation. A recent paper [22] identified distinct metabolic profiles and signaling networks in large-to-giant CMNs, with implications for both malignant potential and novel therapeutic targeting. Our finding of divergent molecular trajectories—particularly in the case with *BRAF* fusion and *PRKR1A* loss—supports the need for precision oncology approaches even in this rare pediatric context.

In conclusion, this case series illustrates the clinical and molecular complexity of melanoma arising in CGMN. While *NRAS*-driven cases appear to follow an aggressive course, molecular outliers with different molecular drivers (e.g. such as *BRAF* fusions or deletion of *PRKAR1A* gene, as for our case #3) emphasize the need for individualized diagnostics and management. DNA methylation profiling, by supporting both accurate classification and CNV analysis, proved instrumental in distinguishing malignant lesions from their benign CGMN counterparts, underscoring the necessity of integrating multi-omic data—particularly epigenomic and genomic features—to achieve a more precise molecular characterization of melanocytic lesions. These results highlight the importance of early molecular characterization to inform clinical decision-making and to guide therapeutic strategies. While some patients received immune checkpoint inhibitors, responses were variable and often transient, and significant immune-related adverse events (irAEs) remain a concern, particularly in pediatric populations. This reinforces the urgent need for more effective and less toxic therapeutic options for children.

Ongoing collaborative efforts, such as prospective registries and multicenter studies, are critical to advancing our understanding and management of this rare disease. In the interim, heightened clinical vigilance, early molecular profiling, and individualized multidisciplinary care remain essential for optimizing outcomes in children with CGMN at risk for malignant transformation.

Author contributions

EM and MDDP conceived the study and drafted the manuscript. MC, FDO, AD, FG, AC, AC, and MCG selected the cases and provided the relevant clinical information, while SR, AS and RA performed histopathological review. LP and FV performed DNA methylation experiments, and SP performed bioinformatics analyses. SB and IG performed RNA sequencing experiments. Finally, AM, FL, RA, MEH and MZ supervised the study and provided critical review. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Bambino Gesù Children's Hospital (Approval No. 202205_INNOV_ONETTI). Written informed consent to participate in this study was obtained from all participants' legal guardians.

Consent for publication

Written informed consent was obtained from the patients' legal guardians for the publication of anonymized clinical details and any accompanying images.

Competing interests

The authors declare no competing interests.

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