

Case Report

Meningeal Melanocytoma - Focus on Molecular Aspects with 3 New Molecular Alterations: A Literature Review and Report of Two Cases

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Abstract

Background: Meningeal melanocytoma (MM) is a locally aggressive, low-grade primary melanocytic tumor of the central nervous system (PMN-CNS). According to the literature, GNAQ and GNA11 mutations are relatively frequent. In contrast, BRAF and NRAS mutations are very rare. Other series have reported BAP1 mutation, monosomy 3 and gain of chromosome 6. In this paper, we discussed two cases of MM for whom a FoundationOne CDx™ assay was performed.

Results: Case report 1: A 48 year old man was diagnosed with intermediate-grade MM based on histological assessment, which is consistent with the clinical evolution. The FoundationOne CDx™ assay detected a SF3B1

mutation, usually found in 15% of uveal melanomas. This mutation is correlated with improved progression-free survival in uveal melanomas. Case report 2: A 39 year old women was diagnosed with MM. Her evolution wasn't expected based on histology only; her history didn't match with rather benign histological features microscopically. The FoundationOne CDx™ assay provided two interesting elements: first, the tumour was positive for CDKN2A p16INK4a M52fs*1 and p14ARF H66fs*106 mutations, most commonly found in cutaneous melanomas. Secondly, a GNA11 Q209L mutation, known to be a marker of aggressiveness in uveal melanoma, was detected.

Conclusion: The identification of molecular alterations in PMN-CNS, in addition to immunohistochemical analysis could provide a better understanding of the biological and clinical behaviour of these tumours, a better identification of melanocytic melanomas with poor prognosis and a high risk of relapse or metastasis, and the development of novel therapeutic options for these patients.

Keywords: Neuro-oncology; Meningeal melanocytoma; Genetic mutation; Case report

Abbreviations: CNS- central nervous system; MM: Meningeal melanocytoma; PMN-CNS- primary melanocytic tumor of the central nervous system; MRI- magnetic resonance imaging; UM- uveal melanoma; IHC- immunohistochemistry; Gry- Grays; NGS- next generation sequencing; TMB- tumor mutation burden; STIR- short inversion recovery; MMR- mismatch repair; MSI- microsatellite instability; pRB- retinoblastoma protein; FA- fanconi anemia; HRRD- homologous recombination repair deficiency

1. Introduction

According to the WHO 2016 classification, primary melanocytic tumors of the central nervous system (PMN-CNS) include meningeal melanocytoma (MM), meningeal melanoma, meningeal melanocytosis and meningeal melanomatosis. MM is a locally aggressive, low-grade PMN-CNS, arising from leptomeningeal melanocytes. These melanocytes derive from multipotent cells migration from the neural crest during embryogenesis [1] and are physiologically located at the highest concentrations in the upper cervical spinal cord and the ventrolateral surface of the medulla oblongata [2]. MM is a very rare disease (1 per 10 million per year), more frequent in females (1,5 : 1 ratio), with a peak incidence in the fifth decade and predilection for the spinal cord and posterior fossa [3-5]. Histologically, melanocytomas correspond to a very limited nodular mass of black or dark brown colour. Microscopic examination shows oval or fusiform cells, with highly pigmented cytoplasm, little cytonuclear atypia, tight nests, vasocentric fascicles and sheet-like arrangements [6] and low proliferative activity (zero to one mitosis per 10 high-power fields (HPFs) and Ki-67 <1-2%) [4]. Intermediate-grade melanocytic tumour shares with malignant melanoma common features of aggressiveness such as increased mitotic activity (1-3 mitoses per 10 HPFs and Ki-67 ranging from 1% to 4%) or microscopic invasion of central nervous system (CNS) structures, but lack cellular atypia found in high-grade lesions [7, 8].

Magnetic resonance imaging (MRI) is particularly interesting for diagnosis and extension assessment, due to the paramagnetic behaviour of the melanin contained in this tumour. It most often corresponds to a solitary extra cranial mass attached to the underlying dura, with a heterogeneous T1 hypersignal, less intense than fat, T2 hyposignal and a moderate increase after injection [9]. MM is often first referred to as meningioma on imaging reports despite different radiological features. The treatment of MM is based on complete surgical resection. Patients with complete surgical excision have good prognosis. In case of incomplete resection or recurrence, adjuvant radiation therapy is recommended and the risk of relapse rises up to 50% one year after surgery [10]. To date, there are no prognostic factors to identify tumours at risk of relapse. Genetic screening could help clinicians to better identify high-grade tumours with a high risk of recurrence. PMN-CNS genetic background remains limited, due to the rarity of these tumors.

According to the literature data, GNAQ and GNA11 mutations are relatively frequent. In contrast, BRAF and NRAS mutations are very rare[9]. Other series have reported BAP1 mutation [11], monosomy 3 and gain of chromosome 6 [12]. Early data show that PMN-CNS are genetically different from cutaneous melanomas and closer to uveal melanomas (UM), although differences exist. Similar to UM, PMN-CNS frequently harbour activating GNAQ or GNA11 mutations [13], but the other mutations described in UM (BAP1, SF3B1 and EIF1AX) [14, 15] are rare in PMN-CNS [9, 11]. In a series of 19 melanocytic tumours of the CNS, Van de Nes et al. described 71% of GNAQ mutations and 12% of GNA11 mutations. In this cohort, the GNA11 mutated tumours were intermediate prognostic MM and relapsed. Twenty nine genes known to be frequently mutated in UM or cutaneous melanomas were analyzed [11]. Other recurrent mutations were not identified.

We present here the genetic sequencing results of 2 patients with MM, one of which presented an aggressive behaviour with leptomeningeal seeding. We used the FoundationOne® test, a next-generation sequencing (NGS) based assay, which identifies genomic alterations within hundreds of cancer-related genes.

2. Method of Sequencing

FoundationOne CDx™ is a NGS assay that allows in-vitro detection of genomic alterations and signatures in more than 300 cancer-related genes. DNA is extracted from formalin-fixed paraffin embedded tumour tissue samples. Whole-genome shotgun library construction and hybridization-based capture of DNA is then processed. Genomic variants are finally detected using custom software. FoundationOne CDx™ assay is routinely relevant in five solid malignant neoplasms: non-small cell lung cancer, breast cancer, melanoma, colorectal cancer and ovarian cancer. Results can help physicians to identify patients likely to benefit from targeted treatments. A list of clinical trials is provided for patients with potentially actionable alterations without therapeutic agent available. Tumour mutation profiling is achievable in all types of cancer.

3. Results

3.1 Case report 1

A 48 years old man consulted in November 2013 for a one-year history of cervicalgia and recent salivation increase appeared progressively. He had neither history of removed melanocytic tumours nor family history of cancer. MRI at baseline revealed a large retro-bulbar lesion with mass effect on medulla oblongata. This lesion was homogenously enhanced after gadolinium injection on T1-weighted imaging (Figure 1a) and hypointense on T2-weighted sequence (Figure 1b). Radiological assessment was compatible with meningioma despite atypical features. Patient underwent surgery to perform total tumour resection. The intraoperative aspect of the tumour, being fibrotic and moderately haemorrhagic was initially supporting the diagnostic of meningioma. Partial surgical resection was performed due to a significant risk of bleeding. Histopathologic finding revealed a highly cellular tumoral proliferation of meningotheliomatous cells (Figure 2a, Figure 2b) with low mitotic activity and a 10% proliferation index (Ki67) (Figure 2c). Immunohistochemistry (IHC) staining for HBM45 and Melan A were both positive in tumour cells cytoplasm (Figure 2d) and heterogenic for S100 protein (Figure 2e). Other melanoma IHC markers assessed were negative. The diagnosis of intermediate-grade MM was made according to the 2016 WHO classification of tumours of the CNS. Adjuvant radiotherapy was discussed in a neuro-oncology multi-disciplinary team, with a total dose of 50.4 Grays (Gy) (28 fractions of 1.8 Gy). Local tumour control was good for 3 years, and the patient got back to work with a good quality of life.

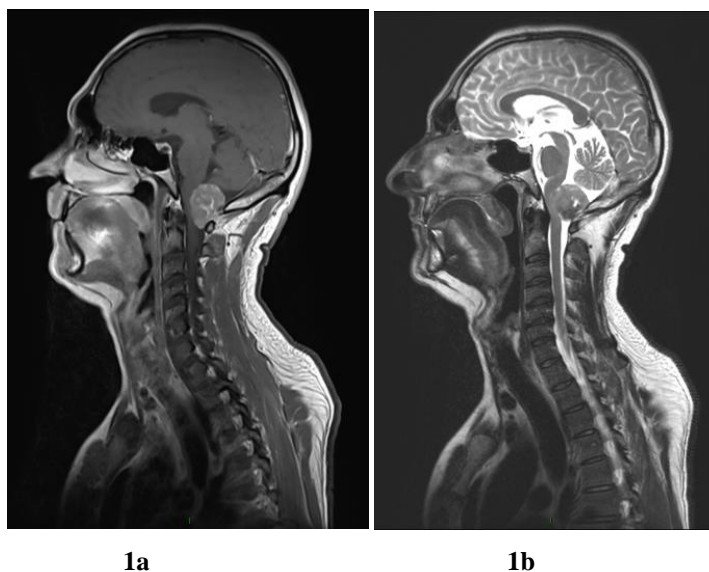


Figure 1: Baseline MRI scan in sagittal plane (case report 1): Gadolinium-enhanced T1-weighted MRI showing a large contrast-enhanced retro-bulbar lesion with mass effect on medulla oblongata (sagittal plane, October 2013) (a) and T2-weighted MRI showing a large hypointense retro-bulbar lesion with mass effect on medulla oblongata (sagittal plane, October 2013) (b).

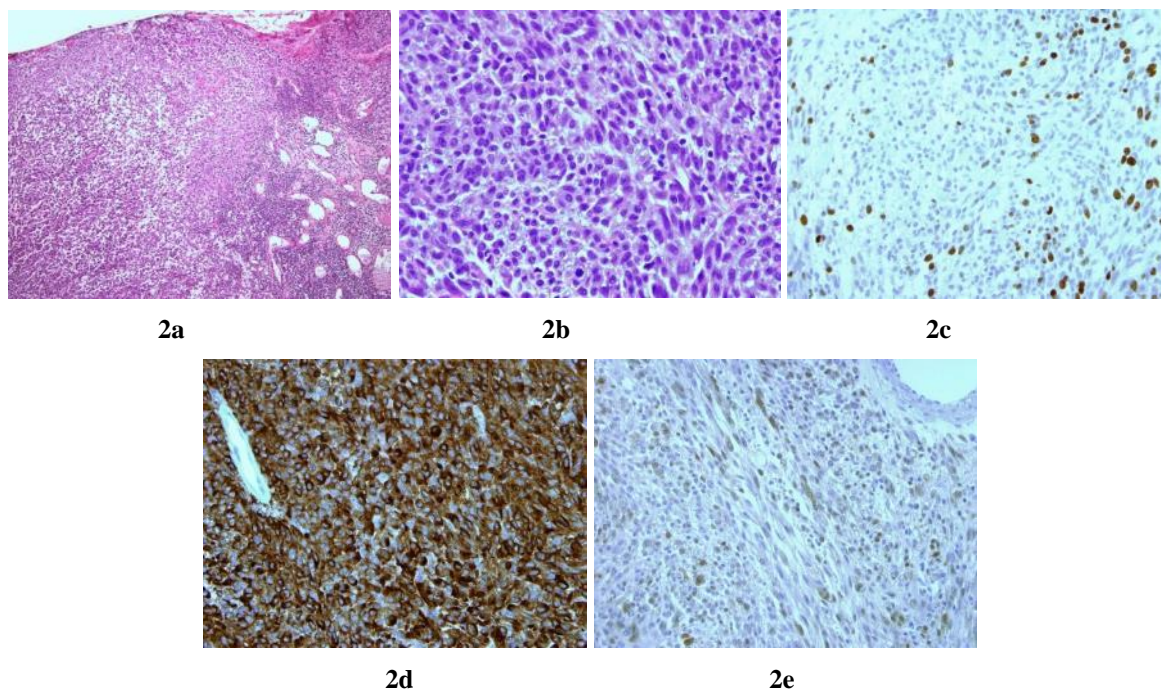


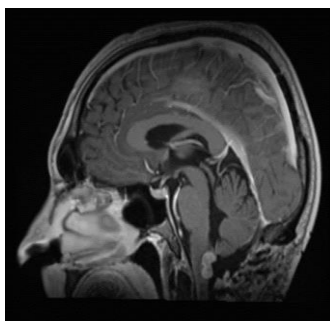
Figure 2: Histopathologic and immunohistochemistry assessment of tumor cells (case report 1): Meningeal infiltration by a highly vascularized melanocytic tumoral proliferation (x10) (a); Meningeal melanocytoma cells with oval and fusiform nuclei (x40) (b); Tumour cells nuclear staining showed a 10% Ki-67 proliferation index (x40) (c); Intense tumour cells cytoplasmic staining for HMB45 and Melan A (x40) (d) and Heterogenic tumour cells cytoplasmic staining for S100 protein (x40) (e).

In August 2016, bilateral and symmetric lower extremities weakness and sphincter disorders appeared progressively. Whole spine MRI revealed a T2-T3 intramedullary nodular lesion compatible with MM metastasis and a progressive retro-bulbar lesion (Figure 3a, Figure 3b). T2-T3 decompressive radiotherapy was performed with a total dose of 30 Gy (10 fractions of 3 Gy). Follow-up MRI in October 2016 revealed a progressive retro-bulbar lesion but a stable intramedullary lesion. In November 2016, after 3 cycles of palliative Temozolomide-based regimen (200 mg/m²), both the retro-bulbar and the intramedullary lesions have progressed. Temozolomide was discontinued and surgical excision was indicated. However, surgery had to be postponed due to patient's professional constraints. In February 2017, a C7-C8 paraesthesia of the left upper limb appeared progressively. Target lesions were stable on MRI. Surgical excision of the intramedullary lesion was performed.

Six months later, in October 2017, the intramedullary lesion increased leading to a second line of Fotemustin-based chemotherapy regimen (100 mg/m²). A FoundationOne CDx™ NGS based assay, evaluating more than 300 cancer-related genes, was performed. Two genomic alterations were described: GNAQ Q209P and SF3B1 R625H. Microsatellite status was stable and tumor mutation burden (TMB) was low (5 Muts /Mb).



3a



3b

Figure 3: Post-treatment MRI scan in sagittal plan 3 years later (case report 1): Contrast-enhanced T2-T3 intramedullary lesion on gadolinium-enhanced T1-weighted whole-spine MRI (sagittal plane, August 2016) (a) and Contrast-enhanced retro-bulbar lesion on gadolinium-enhanced T1-weighted MRI (sagittal plane, August 2016) (b).

3.2 Case report 2

A 66 years old woman was referred in 2014 by her general practitioner to the neurosurgery unit for a two years history of progressive left foot elevators deficiency and numbness of the two first left toes. She had neither history of removed melanocytic tumours nor family history of cancer. Physical examination was consistent with grade-2 left foot elevators deficiency, steppage gait at walk and left lower limb pyramidal syndrome. MRI at baseline revealed a contrast-enhanced T11-T12 intramedullary lesion without intracranial lesion. Electro-neuromyogram confirmed a left grade-3 L5 paresis. A tumour biopsy was performed in October 2015 after a T12-L1 laminectomy. Complete surgical resection was not possible due to a highly haemorrhagic tumour. Histological extemporaneous analysis revealed a meningeal melanocytic tumour. Post-operative MRI, performed in November 2015, showed the residual intramedullary lesion with contrast-enhancement on T1-weighted imaging (Figure 4a, Figure 4b), hypo-intense on short inversion recovery (STIR) T1-weighted imaging (Figure 4c). Histological final analysis revealed a highly cellular tumour (Figure 5a) with tumour cells harbouring elongated, fusiform nuclei and condensed nucleolus (Figure 5b). Two mitoses were spotted. Melanic pigment was highly concentrated in tumour cells cytoplasm (Figure

5c). IHC staining was strongly positive for HMB45 and Melan A (Figure 5d, Figure 5e), finally confirming the diagnostic of MM. Initial extension assessment looking for distant locations was negative. Urinary and faecal incontinence rapidly appeared without saddle block anaesthesia. The patient was treated with IMRT spinal stereotactic radiosurgery with a total dose of 43.369 Gy (25 fractions of 1.735 Gy) in November 2015.

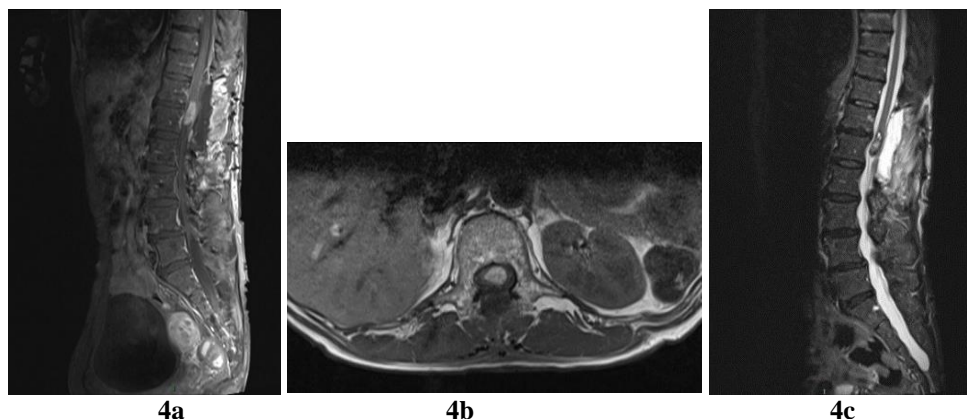


Figure 4: Post-operative MRI scan in sagittal plan (case report 2): T11-T12 contrast-enhanced intramedullary lesion on gadolinium-enhanced T1-weighted MRI (sagittal plane, November 2015) (a); Post-operative T11-T12 contrast-enhanced intramedullary lesion on gadolinium-enhanced T1-weighted MRI (axial plane, November 2015) (b) and Post-operative T11-T12 hypointense lesion on STIR T1-weighted MRI (sagittal plane, November 2015) (c) .

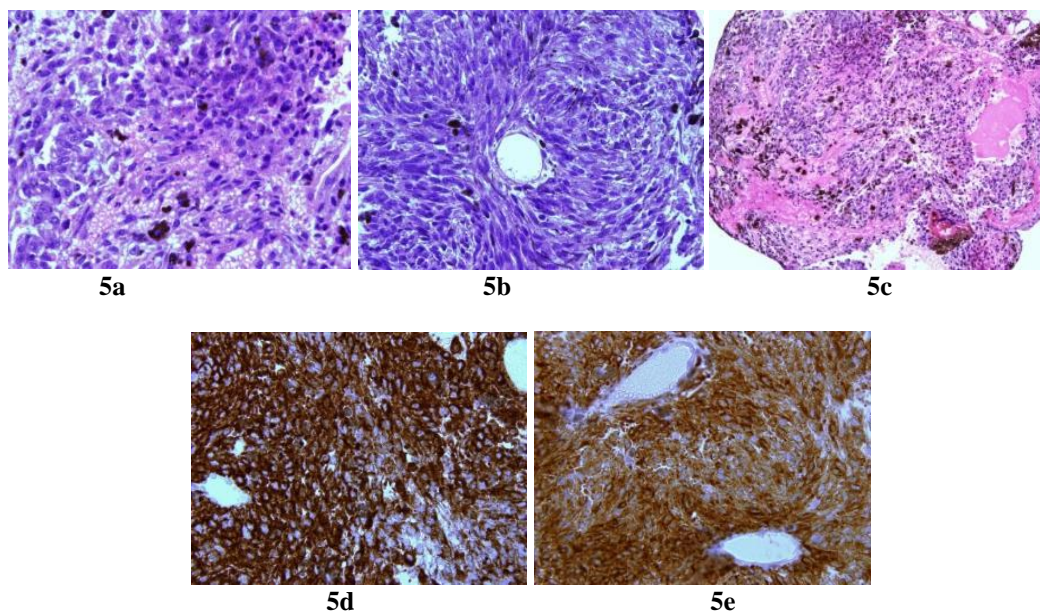


Figure 5: Histopathologic and immunohistochemistry assessment of tumor cells (case report 2): Highly cellular meningeal melanocytoma (x 60) (a); Meningeal melanocytoma cells with elongated nuclei (x 40) (b); Highly pigmented meningeal melanocytoma (X 20) (c); Intense tumour cells cytoplasmic staining for HMB45 (x 60) (d) and Tumour cells cytoplasmic staining for Melan A (x 60) (e).

Six months later, in July 2016, the follow-up MRI showed progression. Total surgical resection was performed in October 2016 with stable disease for 2 years. In January 2018, the patient presented a cauda equina syndrome with progressive left L5 radiculopathy. In February 2018, cognitive impairment and global lower limbs weakness appeared. MRI revealed a meningeal contrast enhancement compatible with carcinomatous leptomeningitis. A FoundationOne CDx™ NGS based assay was performed. However, only best supportive care could be provided due to fast performance status alteration.

Results were positive for three genomic aberrations: GNA11 Q209L, CDKN2A p16INK4a M52fs*1 and p14ARF H66fs*106 and FANCD2 Q802H. Microsatellite status was stable, and TMB was low (1 Mut /Mb).

3.3 Sequencing results

The results of sequencing of both patients are presented in Table 1.

Patients	Genomic alterations	Microsatellite status	Tumor Mutation Burden (TMB)
Patient 1	GNAQ Q209P SF3B1 R625H	Stable	Low (5 Mutations /Mb)
Patient 2	GNA11 Q209L CDKN2A: p16INK4a M52fs*1 p14ARF H66fs*106 FANCD2 Q802H	Stable	Low (1 Mutations /Mb)

Table 1: Sequencing results of patients realised by FoundationOne CDx™.

4. Discussion

4.1 Microsatellite status

Microsatellites are small, non-coding DNA sequences that are randomly distributed in the genome. They are often characterized by repetitions of identical bi-nucleotides. Microsatellites show cellular dysfunction during DNA replication. During DNA replication, base matching errors frequently occur, leading to sequence errors within the replicated DNA. During the normal process, these errors are automatically corrected by a coordinated set of proteins: the proteins of the Mismatch Repair (MMR) system. Because of their repetitive sequence, microsatellites are particularly exposed to replication errors. It most often results in a repetition number of nucleotides not retained (either higher or lower than the original sequence of the microsatellite considered). The protein system of repair errors consists of a family of proteins (MMR system proteins), the main ones being MSH2, MLH1, MSH6, PMS1 and PMS2. The inactivation of MMR protein expression leads to a lack of DNA repair and can contribute to oncogenesis [16].

In this study, both tumour microsatellite statuses were stable. High microsatellite instability (MSI) was found in over 25% metastatic lesions of melanoma [17]. It has been proposed that the immunogenicity of some tumors might be determined by mutational heterogeneity, because any mutation could possibly lead to production of neo-antigens [18]. Then microsatellite status might be a predictor for immunotherapy. Indeed, tumors with the highest amount of somatic mutations, such as malignant melanoma and non-small cell lung cancer have showed positive results with immune checkpoint inhibitors. Therefore, larger studies are necessary to understand the role of MSI in immunotherapy response.

4.2 Tumour mutational burden

TMB represents the number of somatic protein-coding base substitution and insertion/deletion mutations in a tumor specimen. TMB is influenced by exposure to mutagens [19-21] or MSI [22-25]. Both tumours in this study harbour a low TMB. Higher TMB predicts favorable outcome to PD-1/PD-L1 blockade across diverse tumors [26]. In contrast, patients with low TMB levels, less benefit from immune checkpoint inhibitors such as anti-CTLA-4 therapy in melanoma [27] or anti-PD-1 therapy in non-small cell lung cancer [22, 28].

4.3 GNAQ/GNA11

Oncogenic mutations in GNAQ and GNA11 genes are found in all grades PMN-CNS [9, 29-34]. GNA11 and GNAQ encode the protein guanine nucleotide-binding protein G(q) subunit alpha, which is a protein that acts as a modulator of transmembrane signaling and activates phospholipase C [35-37]. Activating mutations in GNAQ and GNA11 in PMN-CNS mainly affect codon 209, known to be a mutational hotspot, and consist of substitution of glutamine to leucine [c.626 A>T (p.(Gln209Leu))] or, less frequently, by substitution to proline [c.626 A>C (p.(Gln209Pro))] [12, 31-33]. Only a single case of spinal melanocytoma with a codon 183 GNAQ mutation {c.548 G>A [p.(Arg183Gln)]} has been described[34]. These mutations result in constitutive activation of the protein guanine nucleotide-binding protein G(q), which permanently activates the MAP kinase pathway via protein kinases C (PKC), thus promoting carcinogenicity [38-40]. Based on published series, GNAQ mutations are present in about 39% of melanocytomas and 17% of primary leptomeningeal melanomas, while GNA11 mutations are present in approximately 17% of melanocytomas (including intermediate-grade melanocytic neoplasms) and 29% of primary leptomeningeal melanomas [9].

The prognostic significance of GNAQ and GNA11 mutations in PMN-CNS is unclear but some studies suggest that GNA11 mutations are correlated with poor prognosis [8]. The rapid pejorative evolution of the second patient is consistent with these data. There are no approved therapies targeting GNAQ activating mutations. Preclinical studies have reported that inhibitors of PKC or MEK may have anti-tumor activity on GNAQ mutated tumors with other targeted agents [41-44].

4.4 SF3B1

SF3B1 mutation has been reported in about 20% of UM and meningeal melanoma [15], adenoid cystic carcinomas of the salivary gland and breast [45, 46], pancreatic carcinoma [47], glioblastoma and renal clear cell carcinoma [48]. Mutated SF3B1 tumours have deregulated splice pattern. This leads to a neomorphic activity that upregulates aberrant mRNA splicing [49]. Small molecules such as spliceostatin A, meamycin and sudemycins can modulate aberrant splicing via SF3B1 inhibition[50]. Maguire et al. showed that spliceostatin A inhibits the growth of SF3B1-mutant breast cancer cell lines compared to wild-type cell lines [51]. It is the first time that a mutation of SF3B1 is described in MM.

In UM, SF3B1 mutations are associated with a good prognosis and primarily occur in tumors which do not metastasize [15]. In this case, the SF3B1 mutation was associated with poor prognosis. Inhibition of SF3B1 could be a future strategy in different types of cancers affected by spliceosome-related genes mutations.

4.5 CDKN2A

CDKN2A encodes two distinct tumor suppressor proteins, p16INK4a and p14ARF [52, 53]. The protein p16INK4a is an inhibitor of the cyclin D-dependent kinases CDK4 and CDK6 that prevents them from phosphorylating the retinoblastoma protein (pRB) and thus stop exit from the G1 phase of the cell cycle [52]. The protein p14ARF is involved in the regulation of p53 pathway [53]. p16-cyclin D-CDK4/6-retinoblastoma pathway amplification is a common early event in primary melanoma. A study to compare the genetic alterations of primary melanomas with their adjacent precursor lesions showed biallel inactivation of CDKN2A exclusively in invasive melanomas [54].

In a series of 143 patients with primary invasive melanoma, Young et al. reported a 56% rate of hemizygous or homozygous loss of CDKN2A [55]. Melanoma cell lines with protein p16INK4a loss through CDK2NA gene deletion or methylation were shown to be more sensitive to Palbociclib (PD0332991) compared to wild-type melanoma cell lines. p16INK4a expression loss already had been shown to predict sensitivity to Palbociclib (PD0332991) in ovarian [56], breast [57] and renal cell carcinoma [58] cell lines. A future clinical trial (NCT03454919) will assess Palbociclib in advanced acral melanoma patients with p16INK4a loss. Another clinical trial (NCT02645149) will assess the efficacy of NGS-guided targeted therapy matched to genetic aberration in patients with BRAF and NRAS wild-type unresectable stage III or IV progressive metastatic melanoma after standard therapies. These studies may provide evidence toward the use of CDK4 inhibitors in treating melanoma based on CDKN2A gene status.

According to the literature, this is the first time that this molecular alteration has been described in MM. The role of p16INK4a expression loss as a predictive response biomarker for Palbociclib in patients with MM will have to be explored in future studies.

4.6 FANCD2

FANCD2 is mutated in 5% of Fanconi anemia (FA) patients. FA is an inherited genomic instability disorder, of autosomal recessive transmission, clinically heterogeneous, involving various developmental abnormalities, early-onset bone marrow failure, and a predisposition to cancer [59]. The disease is manifested by defects in DNA repair, hypersensitivity to DNA crosslinking agents, and a high degree of chromosomal aberrations. The FA pathway comprises 13 disease-causing genes involved in maintaining genomic stability.

The FA pathway employs a unique nuclear protein complex, the FA core complex, whose function is to mono-ubiquitinate the FancD2 and FanCI proteins. The FancD2 ubiquitination is indispensable to formation of DNA repair structures that allow the integrity of the genome to be maintained [60]. FancD2 plays a role in preventing chromatin rupture and loss at the end of cell division by interacting with BRCA1 [61] and BRCA2 [62] and with the ATR signalling pathway [63].

It has been shown that the FA pathway is strongly expressed in metastatic melanoma [64] and that gene expression of fanconi anemia was significantly higher in metastatic melanoma than in normal skin [65]. The FA pathway may be a promising new therapeutic target for the treatment of melanoma. The phase II trial NCT03375307 explores the role of Olaparib in metastatic urothelial cancer with DNA-repair defects, including FANCD2 mutation. Talazoparib is being tested in patients with progressive homologous recombination repair deficiency (HRRD) positive stage IV squamous cell lung cancer in a different phase II trial (NCT03377556). To our knowledge, it is the first case of mutation of the FANCD2 gene reported for a MM.

5. Conclusion

MM is a rare CNS tumour with unaddressed issues. In this report, we discussed two cases of MM for whom a FoundationOne CDx™ assay was performed. GNAQ and GNA11 mutations have already been described in several studies. It is however the first time that SF3B1, CDKN2A and FANCD2 mutations are described in MM. The first patient was diagnosed with intermediate-grade MM based on histological assessment, which is consistent with the clinical evolution. The FoundationOne CDx™ assay detected a SF3B1 mutation, usually found in 15% of UM. This mutation is correlated with improved progression-free survival in UM [66].

The second patient's evolution wasn't expected based on histology only; her history didn't match with rather benign histological features microscopically. The FoundationOne CDx™ assay provided two interesting elements: first, the tumour was positive for CDKN2A p16INK4a M52fs*1 and p14ARF H66fs*106 mutations, most commonly found in cutaneous melanomas. Secondly, a GNA11 Q209L mutation, known to be a marker of aggressiveness in UM, was detected. The identification of molecular alterations in PMN-CNS, in addition to immunohistochemical analysis could provide a better understanding of the biological and clinical behaviour of these tumours, a better identification

of melanocytic melanomas with poor prognosis and a high risk of relapse or metastasis, and the development of novel therapeutic options for these patients.

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Conflict of Interest

We have no conflict of interest to disclose.

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