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CASE REPORT

MEK inhibitors for the treatment of immunotherapy-resistant, AGK-BRAF fusion advanced acral melanoma: a case report and literature review

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Abstract

Purpose Acral melanoma (AM), a rare and aggressive melanoma subtype with poor prognosis, presents unique challenges in treatment due to its distinct molecular and immune characteristics. This case report describes a patient with AM harboring an AGK-BRAF fusion mutation, aiming to explore potential mechanisms of resistance to current treatment modalities.

Methods We analyzed tumor tissue samples from the primary and metastatic lesions of the patient using next-generation sequencing (NGS) for genomic profiling and multiplex immunohistochemistry (mIHC) to assess the immune microenvironment. The patient underwent multiple lines of treatment, including immunotherapy, chemotherapy, and targeted therapy, with their clinical outcomes documented and evaluated.

Results The AGK-BRAF fusion mutation and its reciprocal BRAF-AGK rearrangement were identified in both primary and metastatic tumors. Immune profiling revealed abundant CD8 + T cells, PD-L1 + cells, and CD68 + macrophages localized predominantly in the tumor interstitial region, potentially explaining the poor response to immunotherapy. Despite initial disease stabilization with trametinib and lenvatinib, rapid progression occurred, highlighting tumor heterogeneity and limited efficacy of combined therapies.

Conclusion This case underscores the need for personalized approaches in treating AM, especially those with rare molecular alterations like AGK-BRAF fusion. Insights from genomic and immune profiling may inform future therapeutic strategies to overcome resistance and improve outcomes in this challenging melanoma subtype.

Keywords Acral melanoma · AGK-BRAF fusion · Immunotherapy · Tumor immune microenvironment · MEK inhibitors

Introduction

Melanoma is a tumor resulting from the malignant transformation of melanocytes, which are derived from neural crest cells. In recent decades, its incidence has significantly increased in most countries. Acral melanoma (AM) refers to melanoma originating from the hairless areas of the soles, subungual and palms of the hands. Compared with cutaneous melanoma (CM), AM is highly malignant and invasive and has a poor prognosis [1]. The incidence of AM varies among individuals of different ethnic backgrounds: It is rare in Caucasians [2–4] but higher in others, accounting for 50–58% of all cases of melanoma in Asians [5] and even higher in black people (60–70%) [6]. Although significant progress has been made in the treatment of melanoma, including the development of immunotherapies, patients with AM have derived limited benefit from these advances due to unique biological and molecular characteristics, resulting in a low overall survival rate [7].

Since 2011, several immune checkpoint inhibitors (ICIs), including pembrolizumab and nivolumab, have been approved by the United States FDA or the Chinese National Medical Products Administration for the treatment of melanoma [8]. Recent reports have shown that AM patients generally have a low tumor mutation burden [9, 10], and in terms of the spatial characteristics of the tumor immune

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microenvironment, significantly more $CD8^+$ T cells and M1 macrophages infiltrate their tumor interstitial region [11]. These findings may help explain the low success rate of immune monotherapy against AM, as indicated by studies reporting limited objective response rates and survival outcomes for AM patients treated with anti-PD-1 therapies [12, 13]. However, the clinical application of combination therapy in AM is being actively explored. Dual immunotherapy approaches, such as anti-CTLA4 and anti-PD-1 combination therapy, have shown improved efficacy, with significantly higher objective response rates and overall survival compared to monotherapy [14]. A recent study reported that immunization + chemotherapy + antiangiogenic therapy showed good efficacy in the treatment of advanced AM [15].

BRAF mutations occur in roughly 8% of all cancers, being most common in thyroid cancer (59%) and melanoma (51%) [16]. Although *BRAF* mutation (10–35%) is a common driver mutation in AM, it is far more common in CM (45–50%) [17]. The *BRAF* gene mutations are mainly caused by the transversion of thymidine and adenosine, leading to the $BRAF^{V600E}$ mutation, which accounts for 92% of *BRAF* mutations found in tumors. This is also the main type of mutation targeted by the currently approved BRAF/MEK inhibitors. According to an analysis of a large cohort, BRAF fusions were identified in 14 out of 531 melanomas (2.64%) [18]. There are even fewer reports on the use of BRAF/MEK inhibitor reactions for *BRAF* fusion in AM.

We present the following case in accordance with the CARE reporting checklist. We describe a rare case of AM with an *AGK-BRAF* fusion. The patient progressed after receiving combination immunotherapy, used a MEK inhibitor, and then progressed rapidly. Given the rarity of the *AGK-BRAF* fusion mutation in AM and the poor response of the patient to immunotherapy + MEK inhibitor combination treatment, we used next-generation sequencing (NGS) DNA-seq to analyze genomic mutations and fusion events, and multiplex immunohistochemistry (mIHC) to characterize the immune microenvironment of the patient's tumor tissue to gain insights into its potential drug resistance mechanisms.

Case presentation

The patient was a 40-year-old male. He reported that he had a black nevus on the right plantar 30 years ago, with a size of about 3 mm × 3 mm, which gradually increased to 9 mm × 5 mm over time, with a flat surface, uneven pigment distribution, and no ulcers.

In January 2022, the patient developed right groin pain without obvious cause. Physical examination revealed a tumor in the right groin of 8 cm × 5 cm, with adhesion and fixation with the surrounding tissues and poor mobility. The patient underwent biopsy of the right groin tumor at another hospital, and the pathology suggested melanoma lymph node metastasis (tumor 2). The patient then underwent right plantar tumor resection. Postoperative pathology suggested right plantar melanoma (tumor 1). Genetic testing (81-gene panel NGS-DNA detection) suggested that the tumor had a *NF2* (p.R249K) mutation and *AGK-BRAF* (A2:B8) fusion. After surgery, the patient underwent one cycle of liposomal paclitaxel + carboplatin + bevacizumab injection + toripalimab injection on January 27. The specific dosage is unknown. Grade II gastrointestinal reactions occurred after treatment but improved after symptomatic treatment.

The patient came to our hospital for treatment on February 10. After receiving two cycles of treatment with albumin-paclitaxel (500 mg d1) + carboplatin (600 mg d1) + Bevacizumab (400 mg d1/d15) + toripalimab (240 mg d1, d15 Q28d) starting February 16, the patient developed nausea and vomiting. Gastroenteroscopy suggested esophageal and gastric metastasis. On March 25, CT revealed that the lymph nodes adjacent to the right iliac vessels and right groin were slightly enlarged compared to before, with newly developed liver metastases. At this point, genetic testing (Genecast Biotechnology Co., Ltd., Wuxi, 769-gene large panel NGS sequencing) was performed on tumor 2, whose results confirmed *AGK-BRAF* (A2:B8) gene fusion.

From March 26 to May 15, the patient was treated with trametinib (2 mg QD) combined with Lenvatinib (12 mg QD). The review CT scan on April 25 revealed stable disease, but the review CT scan on May 16 showed progressive disease (PD). The patient underwent one cycle of treatment with temozolomide (350 mg d1-d5) + apatinib (250 mg QD) + camrelizumab injection (200 mg d1, d15 Q28d) on May 16. On June 22, a follow-up CT scan showed that, compared to before, the metastatic lymph nodes near the right groin and iliac vessels were significantly enlarged and the intrahepatic metastatic lesions were enlarged and increased, the assessment suggesting PD. Notably, the inguinal lymph node metastasis had previously shown a response to trametinib + lenvatinib, potentially indicating inter-tumoral heterogeneity. The patient died on June 29. The treatment timeline and the corresponding CT results are shown in Fig. 1.

Mutant gene analysis

In March 2022, two copies of tumor tissues (tumor 1 and tumor 2) and the corresponding paracancerous tissues from the patient were formalin-fixed and paraffin-embedded and then sent again to the CAP-certified laboratory (Genecast Biotechnology Co., Ltd., Wuxi) for NGS of 769 genes (Fig. 2A). DNA was extracted and quantified prior to library preparation by the KAPA Hyper Preparation Kit (Kapa Biosystems, USA). Mutationals were identified using Genome

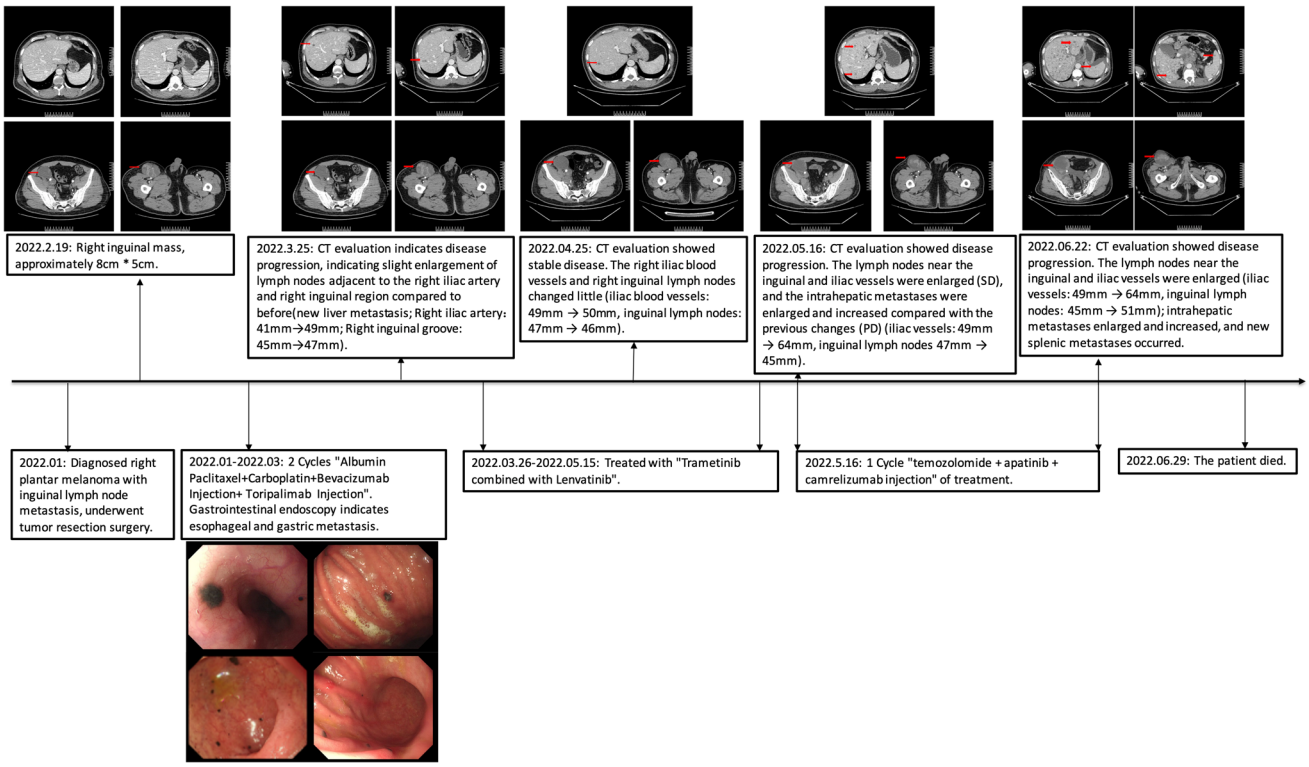


Fig. 1 Treatment timeline and follow-up CT imaging results of the patient

Analysis toolkit (GATK) (v. 3.7), and visualized by the R software program (version 3.6.1, https://www.r-project.org/).

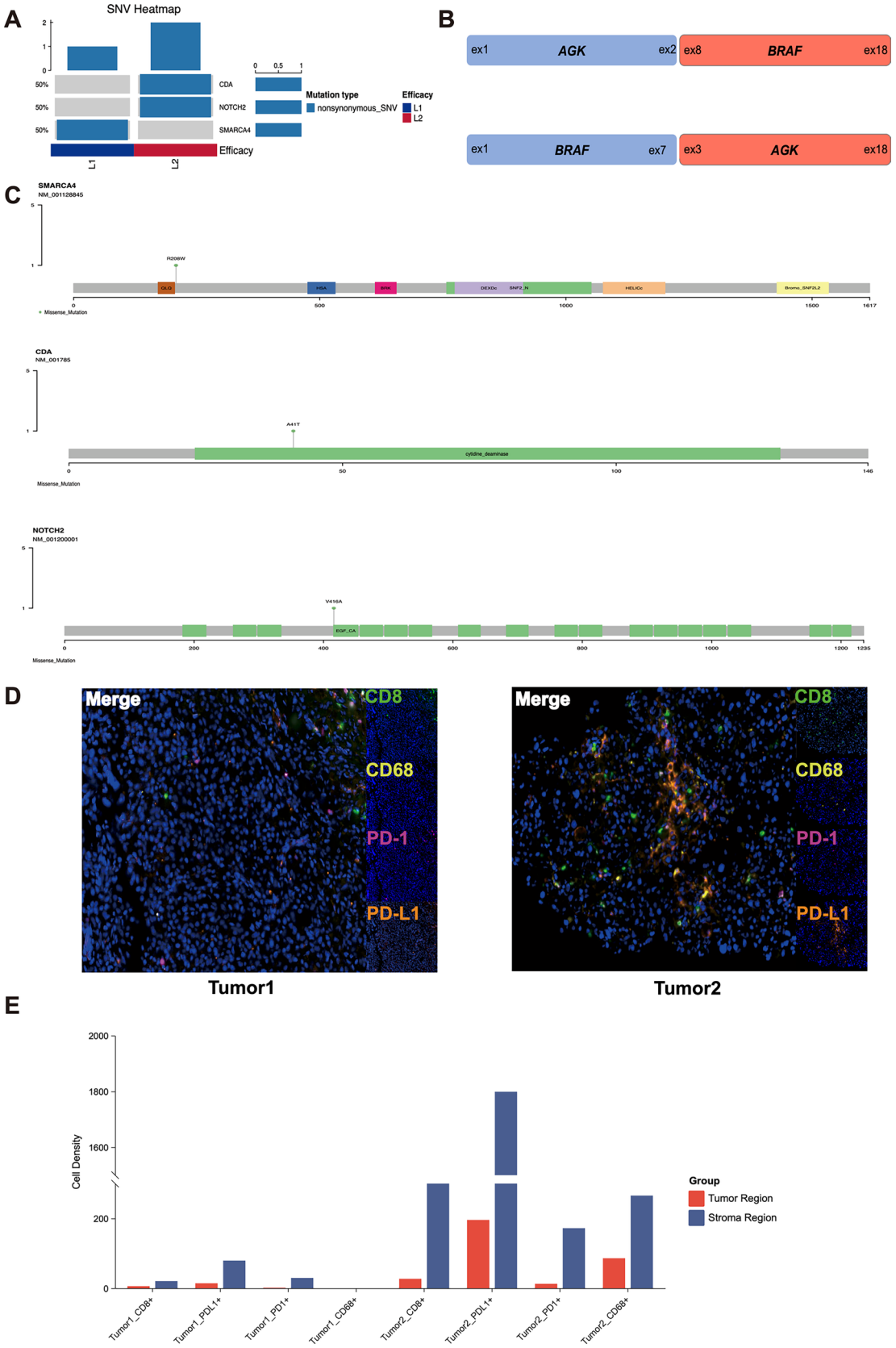
In contrast to the results obtained by the previous assays, *AGK-BRAF* (A2:B8) (1.68%, 4.76%) fusion as well as *BRAF-AGK* (B7:A3) (5.98%, 10.22%) rearrangements were detected in both primary tumor 1 and metastatic tumor 2 by this assay (Fig. 2B). These findings are consistent with the mechanism of an inversion event, which leads to the generation of both *AGK-BRAF* and its reciprocal *BRAF-AGK* fusion [19]. Moreover, the *SMARCA4* p.R208W (2.38%) mutation was detected in tumor 1, and the *NOTCH2* p.V416A (22.64%) and *CDA* p.A41T (29.37%) mutations were detected in tumor 2 (Fig. 2C). Before this, only *AGK-BRAF* (A2:B8) fusion and *NF2* mutations were detected in tumor 1. In addition, we performed analysis on tumor mutation burden and microsatellite instability status and found that both tumor 1 and tumor 2 were microsatellite-stable and microsatellite instability-low.

Multiplex immunohistochemistry

To further explore the immune microenvironments of tumor 1 and tumor 2, mIHC staining was performed using four classic immune microenvironment markers: CD8, PD-L1, PD-1, and CD68. Multiplex immunofluorescence staining was conducted using the Akoya OPAL Polaris 7-Color Automation IHC kit (NEL871001KT) according to the manufacturer's protocol. The primary antibodies used were as follows: CD8 (Zsbio, 1:100 dilution), PD-L1 (CST, 1:100 dilution), PD-1 (Zsbio, 1:50 dilution), and CD68 (Zsbio, 1:500 dilution). Staining was performed using a TSA method. Slides were scanned using the AKoya Vectra imaging system. The quantities of various cell populations were expressed as the number of stained cells per square millimeter and further as the percentage of positively stained cells. The assay results (Fig. 2D) showed that, compared to tumor 1, the immune microenvironment of tumor 2 was more abundant in immune cells, particularly PD-L1 + cells, CD8 + T cells, and CD68 + macrophages. However, it is worth noting that in both tumor 1 and tumor 2, immune cells were predominantly localized to the interstitial region of the tumor rather than the tumor cell area (Fig. 2E). This distribution pattern may have contributed to the poor immunotherapeutic outcome of the patient, despite the immune microenvironment being rich in immune cells.

Discussion and literature review

Compared to CM, AM is more malignant, invasive, and associated with a poorer prognosis. The 5-year survival rate for AM ranges from 62.4 to 77.9%, while for CM,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SNV Heatmap
CDA
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L1
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CD68
PD-1
PD-L1
Tumor1
Tumor2
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Cell Density
Group
Tumor Region
Stroma Region
Tumor1_CD8+
Tumor1_PDL1+
Tumor1_PD1+
Tumor1_CD68+
Tumor2_CD8+
Tumor2_PDL1+
Tumor2_PD1+
Tumor2_CD68+

◂**Fig. 2** The NGS results and immunohistochemical results of the patients two lesions, right plantar melanoma (L1) and melanoma lymph node metastasis (L2). **A** Heatmap of single-nucleotide mutations in L1 and L2 lesions. **B** Fusion and rearrangement events detected in the two lesions. **C** Lollipop plots showing the mutated gene loci in the two lesions. **D** mIHC images showing the expression of CD8, CD68, PD-1, and PD-L1 and the merged image of tumor 1 and tumor 2. **E** Bar graphs illustrating the cell densities of $CD8^+$, $CD68^+$, $PD\text{-}L1^+$, and $PD\text{-}1^+$ cells in the tumor area and stromal area of tumor 1 and tumor 2

it is significantly higher, ranging from approximately 88.9–96.7%, depending on the population and region [20–22]. There is little evidence from large international cohort studies on treatments for metastatic AM. In China, melanoma has a relatively low overall incidence of 0.37 per 100,000 population. However, AM accounts for a higher proportion of melanoma cases in China due to the predominance of acral and mucosal subtypes, compared to other melanoma subtypes commonly seen in Western countries [23].

In recent years, significant progress has been made in the treatment of melanoma. However, as a distinct subtype, AM patients in China have derived limited benefits from traditional treatments like interferon and chemotherapy [12, 24, 25]. Immunotherapy has emerged as a promising option for metastatic melanoma [8], but the efficacy of single ICIs in treating metastatic AM remains suboptimal (Table 1). Clinical studies of PD-1 monoclonal antibody monotherapy for second-line treatment of advanced melanoma in China reported low objective response rates (ORRs) for AM patients, at 15.8% [13, 26] and 14.3% [27], respectively, with OS of 14.8 and 16.9 months, respectively.

To address these challenges, immune combination therapies have gained traction as a development trend in solid tumor treatments, including AM. Among these, dual immunotherapy, combining anti-PD-1 and anti-CTLA-4 agents, appears most effective. In a study of untreated patients with unresectable stage III/IV or recurrent melanoma, the ORR for AM patients treated with nivolumab plus ipilimumab reached 42.9% [28]. Similarly, Nathan et al. reported a median OS of 25.8 months and an 18-month OS rate of 59.0% in AM patients receiving nivolumab after progression on ipilimumab [29]. These findings suggest that dual immunotherapy significantly improves OS and ORR in AM patients, underscoring its potential as a preferred strategy for this challenging melanoma subtype.

The effect of radiotherapy combined with immunity in AM is poor, with a response rate (RR) and disease control rate (DCR) of 0% and 66.6%, respectively [30]. There is little research on immunotherapy combined with chemotherapy. In addition to directly inhibiting tumor cell synthesis, chemotherapy drugs can promote the release and recognition of tumor antigens, upregulate PD-L1 expression, and enhance the efficacy of immunotherapy. Conversely, immunotherapy can rebuild the patient's immune system, protect body homeostasis, and enhance chemotherapy efficacy by activating CD8 + T cells. The results of a domestic multi-center retrospective analysis of pembrolizumab combined with temozolomide in the treatment of unresectable and advanced melanoma showed that the pembrolizumab combined with temozolomide group had a DCR of 80.0%, an ORR of 40%, and a median PFS (mPFS) of 9.8 months. Notably, among the 69 melanoma patients included in the study, 28 (40.6%) were acral melanoma (AM) cases. The results demonstrated that the ORR of the pembrolizumab combined with temozolomide group was significantly higher than that of the pembrolizumab group and chemotherapy group [31]. Anti-angiogenic drugs, such as lenvatinib, can reduce tumor blood supply and block tumor growth, potentially enhancing the efficacy of immunotherapy. By altering the tumor microenvironment, these drugs may modulate immune cell infiltration and improve responses to PD-1 inhibitors. Results from the LEAP-004 study demonstrated the efficacy of combining immunotherapy with anti-angiogenic agents for late-line treatment of advanced melanoma [32]. The study included patients with unresectable, stage III or stage IV disease who had previously received PD-1/PD-L1 monotherapy or multiple lines of combined therapy. The ORR of the overall population was 21.4%, and the DCR was 66%. Among them, 29 patients whose disease progressed after receiving PD-1/PD-L1 antibody combined with CTLA-4 antibody treatment had an ORR of 31%. Recently, an immunotherapy and antiangiogenic study evaluated the efficacy of Camrelizumab combined with Apatinib in the treatment of advanced AM. The results showed that an ORR of 24.1%, with a median PFS and OS were 7.39 and 13.27 months, respectively [33]. Another study of Camrelizumab combined with Apatinib and Temozolomide in the first-line treatment of advanced AM showed that the ORR was 64.0%, and the median time to response and duration of response (DOR) were 2.7 months and 17.5 months, respectively. The DCR was 88.0%, and the estimated median PFS was 18.4 months [15]. When the patient came to our hospital for treatment, we also chose the mode of chemotherapy combined with immune and targeted therapy. Unfortunately, this patient did not respond well to this modality.

Based on the mIHC results of patient's tumor 1 and tumor 2, the reasons for the patient's insensitivity to immunotherapy were further explored. In January 2017, Chen proposed classifying tumors into 3 phenotypes: immune-inflammatory, immune- exclude, and immune-desert. Immune-excluding tumor (IET) refers to the presence of many immune cells around the tumor cells, but immune cells cannot infiltrate the tumor cell core but are restricted to the peripheral stroma of the tumor [34]. Clinically, IET responds little to none to ICIs. The root cause is the inability

Table 1 Summary of immunotherapy clinical trials involving sub-analysis of patients with acral melanoma

PMID	Study	Patients (*N*)	Treatment (line of therapy)	Results	Biomarkers
31445199	Paul Nathan et al. [29]	*n* = 1008 (total) *n* = 55 (AM)	Nivolumab (2+)	Median OS: 25.8 months 18-month OS rates: 59.0%	Not reported
36304457 30981094	Lu Si et al. [13, 26]	*n* = 103 (total) *n* = 39 (AM)	Pembrolizumab (2)	ORR: 15.8% PFS: 2.8 months OS: 14.8 months	PD-L1 positive: PFS: 4.4 months; OS: 22.8 months PD-L1 negative: PFS: 2.7 months; OS: 8.4 months BRAF wild-type: PFS: 3.4 months; OS: 18.5 months BRAF mutant: PFS: 1.9 months; OS: 5.8months
32321714	Bixia Tang et al. [27]	*n* = 128 (total) *n* = 50 (AM)	Toripalimab (2)	ORR: 14.0% Median PFS: 3.2 months Median OS: 16.9 months	Total: PDL1 positive: ORR: 38.5%; PFS: 7.7 months; OS: Not Reached PDL1 negative: ORR: 11.9%; PFS: 2.7 months; OS: 14.4 months NRAS mutations: ORR: 6.3% CCDN1 amplifications: ORR: 0%
30447539	Namikawa et al. [28]	*n* = 30 (total) *n* = 7 (AM)	Ipilimumab + Nivolumab (1)	ORR: 42.9%	Not reported
30758859	Junji et al. [30]	*n* = 10 (total) *n* = 3 (AM)	Nivolumab/pembrolizumab + radiotherapy (mixed)	ORR: 0%	Not reported
36753834	Xuan Wang et al. [33]	30	Camrelizumab + Apatinib (1)	ORR:24.1% Median PFS: 7.39 months Median OS: 13.27months	A 5-gene set (TTN, MUC16,VPS13D, ALPK2 and SCUBE1), Patients with gene-set positive showed markedly better PFS and OS than those with gene-set negative in this cohort

of cytotoxic T lymphocytes to effectively infiltrate tumors. In our case report, although patient's tumor 2 had high PD-L1 expression and $CD8^+$ cell staining, the staining had a limited range, being concentrated in the tumor interstitial area, and the expression of all immune indicators in tumor 1 was very low. This may help explain the patient's poor response to immunotherapy despite some immune cell expression within the immune microenvironment.

The combination of anti-PD-1 therapy with chemotherapies, such as paclitaxel and carboplatin, or temozolomide in the first line of treatment may have detrimental effects on the establishment of an effective immune response, as suggested by some studies [35]. Furthermore, the use of anti-VEGF agents, such as bevacizumab, may contribute to the immune-excluding tumor (IET) phenotype by inhibiting blood vessel formation, which can impair the infiltration of immune cells into the tumor. However, this area remains controversial, and it is important to draw cautious conclusions, particularly in the context of a single case report.

A team from Fudan University published a report in the journal *Nature Communications* on a type of antifibrotic small molecule-based nanoparticle, which encapsulates plasmids that can encode immunostimulatory cytokines. This nanosystem acts as a cytotoxic T lymphocyte infiltration enhancer, which can induce intratumoral vascular normalization and stimulate the release of T-lymphocyte recruitment signals by weakening the stromal barrier within the IET, thereby increasing the infiltration level of cytotoxic T-lymphocytes within the IET and ultimately improving the response to ICIs within the IET [36]. This may become a novel treatment mode for IET melanoma.

In addition to the AGK-BRAF fusion, mutations in SMARCA4 (p.R208W), CDA (p.A41T), NOTCH2 (p.V416A), and NF2 (p.R249K) were detected. SMARCA4 mutations have been implicated in various cancers, including small cell lung cancer, where they are associated with poor prognosis [37]. NOTCH2 mutations are known to play a role in various malignancies, including glioma and lymphoma, suggesting potential oncogenic properties [38]. NF2 mutations, which are well-known in the context of neurofibromatosis type 2, have also been implicated in other tumor types, including meningiomas and schwannomas [39].

To further explore more effective treatment models, we focused on the rare AGK-BRAF fusion detected in this patient. BRAFV600E occurs in the kinase activation region of BRAF exon 15, leading to spontaneous, sustained, and aberrant activation of the MAPK pathway. Unlike the BRAFV600E mutation, which involves an activating mutation within the kinase domain, the AGK-BRAF fusion retains the wild-type kinase domain but lacks the CR1 domain, which includes the autoinhibitory region. This loss of the autoinhibitory domain results in constitutive activation of the MAPK pathway through autophosphorylation. This structural difference impacts the conformation and activation state of the kinase, influencing its responsiveness to inhibitors [18, 40, 41].

In 2022, a case of soft tissue myoepithelial carcinoma with *AGK-BRAF* fusion was reported. Although chemotherapy and regorafenib treatment did not result in significant remission, the use of MEK inhibitor cobimetinib as a monotherapy resulted in sustained clinical response [42]. Although reports of MEK inhibitors (MEK-TKIs) treating melanoma with BRAF fusions are rare, some cases exist. A cutaneous melanoma with PPFIBP2-BRAF fusion and an acral melanoma with KIAA1549-BRAF fusion responded to MEK inhibitors[43]. Other examples include a BRAF-ZKSCAN5 fusion responding to dabrafenib and trametinib and a SKAP2-BRAF fusion resistant to immunotherapy but sensitive to MEK inhibitors [44, 45]. However, not all BRAF fusions are sensitive, as shown by a FNBP1-BRAF fusion resistant to both immunotherapy [46].

The case presented in this report highlights a rare AGK-BRAF fusion in acral melanoma (AM) that demonstrated only transient disease stabilization with MEK-TKI therapy (trametinib and lenvatinib), followed by rapid progression in some metastases. This suggests the potential influence of tumor heterogeneity and the challenges of targeting BRAF fusions in AM.

Conclusions

This case report describes a patient with AM harboring an AGK-BRAF fusion. The patient initially achieved stable disease with trametinib and lenvatinib but subsequently experienced rapid disease progression, particularly in some metastases, indicating intertumoral heterogeneity. Through NGS and mIHC, we characterized the genomic landscape and immune microenvironment of the tumor. The limited response to immunotherapy might be attributed to the immune-excluding tumor (IET) phenotype observed in the microenvironment.

While this case suggests that MEK inhibitor therapy may provide temporary stabilization in AGK-BRAF fusion-driven AM, the advanced stage of disease at the time of treatment might have limited its efficacy. Further studies are needed to explore the heterogeneity of BRAF fusions and assess the effectiveness of MEK inhibitors at earlier stages of disease. This single case highlights the complexities of treating AM with rare genetic alterations like AGK-BRAF fusion and underscores the need for personalized therapeutic approaches.

Author contributions Conception and design: Yanling Zhang, Xifeng Zhang, Weikang Shao, Xianbin Liang; (II) Administrative support: Yan Wang, Xianbin Liang; (III) Provision of study materials or patients: Ji Gao, Mei Xiang, Yan Wang, Xianbin Liang; (IV) Collection and assembly of data: Ji Gao, Mei Xiang, Yan Wang, Xianbin Liang; (V) Data analysis and interpretation: Yanling Zhang, Mengmeng Liu, Weizhen Zhang, Xianbin Liang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All author.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflcit of interest Author Weikang Shao is employed by Genecast Biotechnology Co.Ltd. The remaining authors have no relevant financial or non-financial interests to disclose.

Ethics statement The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. The studies involving human participants were reviewed and approved by Ethics Committee of The Third People's Hospital of Zhengzhou.

References

1. Wei X, Wu D, Li H, Zhang R, Chen Y, Yao H et al (2020) The clinicopathological and survival profiles comparison

across primary sites in acral melanoma. Ann Surg Oncol 27(9):3478–3485
2. Cascinelli N, Zurrida S, Galimberti V, Bartoli C, Bufalino R, Del Prato I et al (1994) Acral lentiginous melanoma. A histological type without prognostic significance. J Dermatol Surg Oncol 20(12):817–822
3. Cormier JN, Xing Y, Ding M, Lee JE, Mansfield PF, Gershenwald JE et al (2006) Ethnic differences among patients with cutaneous melanoma. Arch Intern Med 166(17):1907–1914
4. Shaw JH, Koea JB (1988) Acral (volar-subungual) melanoma in Auckland, New Zealand. Br J Surg 75(1):69–72
5. Chang JW (2013) Acral melanoma: a unique disease in Asia. JAMA Dermatol 149(11):1272–1273
6. Hudson D, Krige J (1995) Melanoma in black South africans. J Am Coll Surg 180(1):65–71
7. Bhave P, Ahmed T, Lo SN, Shoushtari A, Zaremba A, Versluis JM et al (2022) Efficacy of anti-PD-1 and ipilimumab alone or in combination in acral melanoma. J Immunother Cancer. 10(7):e004668
8. Leonardi GC, Candido S, Falzone L, Spandidos DA, Libra M (2020) Cutaneous melanoma and the immunotherapy revolution (review). Int J Oncol 57(3):609–618
9. Shi Q, Liu L, Chen J, Zhang W, Guo W, Wang X et al (2022) Integrative genomic profiling uncovers therapeutic targets of acral melanoma in Asian populations. Clin Cancer Res 28(12):2690–2703
10. Yeh I, Jorgenson E, Shen L, Xu M, North JP, Shain AH et al (2019) Targeted genomic profiling of acral melanoma. J Natl Cancer Inst 111(10):1068–1077
11. Huang R, Shen G, Ren Y, Zheng K, Wang J, Shi Y et al (2023) Prognostic value of genetic aberrations and tumor immune microenvironment in primary acral melanoma. J Transl Med 21(1):78
12. Yi JH, Yi SY, Lee HR, Lee SI, Lim DH, Kim JH et al (2011) Dacarbazine-based chemotherapy as first-line treatment in noncutaneous metastatic melanoma: multicenter, retrospective analysis in Asia. Melanoma Res 21(3):223–227
13. Si L, Zhang X, Shu Y, Pan H, Wu D, Liu J et al (2022) Pembrolizumab in Chinese patients with advanced melanoma: 3-year follow-up of the KEYNOTE-151 study. Front Immunol 13:882471
14. Carlino MS, Larkin J, Long GV (2021) Immune checkpoint inhibitors in melanoma. Lancet 398(10304):1002–1014
15. Mao L, Lian B, Li C, Bai X, Zhou L, Cui C et al (2023) Camrelizumab plus apatinib and temozolomide as first-line treatment in patients with advanced acral melanoma: the CAP 03 phase 2 nonrandomized clinical trial. JAMA Oncol 9(8):1099–1107
16. Holderfield M, Deuker MM, McCormick F, McMahon M (2014) Targeting RAF kinases for cancer therapy: BRAF-mutated melanoma and beyond. Nat Rev Cancer 14(7):455–467
17. Newell F, Wilmott JS, Johansson PA, Nones K, Addala V, Mukhopadhyay P et al (2020) Whole-genome sequencing of acral melanoma reveals genomic complexity and diversity. Nat Commun 11(1):5259
18. Botton T, Talevich E, Mishra VK, Zhang T, Shain AH, Berquet C et al (2019) Genetic heterogeneity of BRAF fusion kinases in melanoma affects drug responses. Cell Rep 29(3):573–588 e7
19. Botton T, Passeron T, Rocchi S (2020) Comment on 'Testing for BRAF fusions in patients with advanced BRAF/NRAS/KIT wild-type melanomas permits to identify patients who could benefit of anti-MEK targeted therapy'. J Clin Pathol 73(8):524–525
20. Bian SX, Hwang L, Hwang J, Ragab O, In GK, Peng D et al (2021) Acral lentiginous melanoma-population, treatment, and survival using the NCDB from 2004 to 2015. Pigment Cell Melanoma Res 34(6):1049–1061
21. Helkkula T, Christensen G, Mikiver R, Ingvar Å, Isaksson K, Nielsen K (2024) Acral melanoma incidence and survival trends in 1990–2020: a nationwide, population-based study. Acta Derm Venereol 104:adv40242
22. Zheng S, Yu H, Zheng X, Wu UT, Ming WK, Huang H et al (2023) Analysis and prediction of 5-year survival in patients with cutaneous melanoma: a model-based period analysis. Front Endocrinol (Lausanne) 14:1238086
23. Han B, Zheng R, Zeng H, Wang S, Sun K, Chen R et al (2024) Cancer incidence and mortality in China, 2022. J Natl Cancer Cent 4(1):47–53
24. Wheatley K, Ives N, Hancock B, Gore M, Eggermont A, Suciu S (2003) Does adjuvant interferon-α for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. Cancer Treat Rev 29(4):241–252
25. Mao L, Si L, Chi Z, Cui C, Sheng X, Li S et al (2011) A randomised phase II trial of 1 month versus 1 year of adjuvant high-dose interferon α-2b in high-risk acral melanoma patients. Eur J Cancer 47(10):1498–1503
26. Si L, Zhang X, Shu Y, Pan H, Wu D, Liu J et al (2019) A phase ib study of pembrolizumab as second-line therapy for Chinese patients with advanced or metastatic melanoma (KEYNOTE-151). Transl Oncol 12(6):828–835
27. Tang B, Chi Z, Chen Y, Liu X, Wu D, Chen J et al (2020) Safety, efficacy, and biomarker analysis of toripalimab in previously treated advanced melanoma: results of the POLARIS-01 multicenter phase II trial. Clin Cancer Res 26(16):4250–4259
28. Namikawa K, Kiyohara Y, Takenouchi T, Uhara H, Uchi H, Yoshikawa S et al (2018) Efficacy and safety of nivolumab in combination with ipilimumab in Japanese patients with advanced melanoma: an open-label, single-arm, multicentre phase II study. Eur J Cancer 105:114–126
29. Nathan P, Ascierto PA, Haanen J, Espinosa E, Demidov L, Garbe C et al (2019) Safety and efficacy of nivolumab in patients with rare melanoma subtypes who progressed on or after ipilimumab treatment: a single-arm, open-label, phase II study (CheckMate 172). Eur J Cancer 119:168–178
30. Kato J, Hida T, Someya M, Sato S, Sawada M, Horimoto K et al (2019) Efficacy of combined radiotherapy and anti-programmed death 1 therapy in acral and mucosal melanoma. J Dermatol 46(4):328–333
31. Hu T, Sun W, Xu Y, Qu X, Jin Y, Luo Z et al (2021) Combination of pembrolizumab plus temozolomide therapy in unresectable and advanced melanoma: a multicenter retrospective analysis in China. Ann Transl Med 9(21):1625
32. Fernandez AA, O'Day S, De la Cruz Merino L, Petrella T, Jamal R, Ny L et al (2020) LBA44 Lenvatinib (Len) plus pembrolizumab (pembro) for advanced melanoma (MEL) that progressed on a PD-1 or PD-L1 inhibitor: initial results of LEAP-004. Ann Oncol 31:S1173
33. Wang X, Wu X, Yang Y, Xu W, Tian H, Lian B et al (2023) Apatinib combined with camrelizumab in advanced acral melanoma patients: an open-label, single-arm phase 2 trial. Eur J Cancer 182:57–65
34. Chen DS, Mellman I (2017) Elements of cancer immunity and the cancer–immune set point. Nature 541(7637):321–330
35. Tran TT, Caulfield J, Zhang L, Schoenfeld D, Djureinovic D, Chiang VL et al (2023) Lenvatinib or anti-VEGF in combination with anti-PD-1 differentially augments antitumor activity in melanoma. JCI Insight 8(7):e157347
36. Huang Y, Chen Y, Zhou S, Chen L, Wang J, Pei Y et al (2020) Dual-mechanism based CTLs infiltration enhancement initiated by Nano-sapper potentiates immunotherapy against immune-excluded tumors. Nat Commun 11(1):622
37. Peng L, Li J, Wu J, Xu B, Wang Z, Giamas G et al (2021) A Pan-cancer analysis of SMARCA4 alterations in human cancers. Front Immunol 12:762598

38. Xiu MX, Liu YM (2019) The role of oncogenic Notch2 signaling in cancer: a novel therapeutic target. Am J Cancer Res 9(5):837–854
39. Bachir S, Shah S, Shapiro S, Koehler A, Mahammedi A, Samy RN et al (2021) Neurofibromatosis type 2 (NF2) and the implications for vestibular schwannoma and meningioma pathogenesis. Int J Mol Sci 22(2):690
40. Turner JA, Bemis JG, Bagby SM, Capasso A, Yacob BW, Chimed T-S et al (2019) BRAF fusions identified in melanomas have variable treatment responses and phenotypes. Oncogene 38(8):1296–1308
41. Botton T, Yeh I, Nelson T, Vemula SS, Sparatta A, Garrido MC et al (2013) Recurrent BRAF kinase fusions in melanocytic tumors offer an opportunity for targeted therapy. Pigment Cell Melanoma Res 26(6):845–851
42. Domen A, Van Paesschen C, Zwaenepoel K, Lambin S, Pauwels P, Rasschaert M et al (2022) Excellent response to MEK inhibition in an AGK-BRAF gene fusion driven carcinoma: case report and literature review. Anticancer Res 42(1):373–379
43. Menzies AM, Yeh I, Botton T, Bastian BC, Scolyer RA, Long GV (2015) Clinical activity of the MEK inhibitor trametinib in metastatic melanoma containing BRAF kinase fusion. Pigment Cell Melanoma Res 28(5):607–610
44. Kato H, Kano S, Yasui Y, Nojiri Y, Yoshimitsu M, Nakamura M et al (2023) Effectiveness treatment of a BRAF-ZKSCAN5 fusion gene melanoma case with dabrafenib/trametinib. Case Rep Oncol 16(1):1007–1012
45. Chew SM, Lucas M, Brady M, Kelly CM (2021) SKAP2-BRAF fusion and response to an MEK inhibitor in a patient with metastatic melanoma resistant to immunotherapy. BMJ Case Rep 14(6):e238494
46. Kervarrec T, Jean-Jacques B, Pissaloux D, de la Tirode F, Fouchardière A (2021) FNBP1-BRAF fusion in a primary melanoma of the lung. Pathology 53(6):785–788

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