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RAPID COMMUNICATION

Clinical management of a rare melanoma case arising from congenital melanocytic nevus

Congenital melanocytic nevi (CMNs) are skin lesions characterized by benign melanocytic proliferations and present at birth or shortly thereafter. Large and giant CMNs, with a projected adult size $\geq$ 20 cm and 40 cm in diameter respectively, are more likely to develop into malignant melanoma. In most cases, melanoma arising from congenital melanocytic nevus (CMN) is particularly aggressive.[1] Meanwhile, there are no standard recommended guidelines specific to the treatment of CMN. Due to the extensive tumor size, complete removal of the plague is difficult. Less invasive treatment options are urgently needed. It is estimated that about 80% of CMNs and 95% of giant CMNs carry *NRAS*-activating mutations.[2] However, targeting mutant *NRAS* is still not feasible. Since *NRAS* mutations can constitutively activate the mitogen-activated protein kinase (MAPK) pathway and fuel melanocytes proliferation and transformation, targeting MAPK kinase (MEK), the key downstream of the MAPK pathway, becomes a feasible treatment strategy for CMN. Indeed, there have been sporadic reports showing that trametinib, a MEK inhibitor, was effective in patients with mutant *NRAS*-driven central nervous system melanoma and giant CMNs.[2,3] However, whether CMN patient is responsive to MEK inhibitor is still unknown. Here, we report a 2-year-old CMN patient carrying an *NRAS*-activating mutation with an objective response to trametinib.

The patient, a Chinese boy, was born with black plaques on the middle back (Fig. 1A). He was healthy during pregnancy and parturition. No melanoma or any other skin disorders history was found in his family. An increase in the size and thickness of the plaques was observed when he was 1.5 years old. At the age of 2 years and 7 months, the largest plaque was about 10 cm $\times$ 4 cm in size and was continuously growing. The boundary of the plaque was unclear with multiple satellite nevi (classified as "L1, middle back, S1, C1, R2, N1, and H0") (Fig. 1A). Surgical resection was performed, and the boy was pathologically diagnosed with MCM (nodular type, Clark V, Breslow 6.7 mm, no ulcer on the surface, no tumor involvement at the basal and lateral margin, Melan-A$^+$, HMB45$^+$, SOX-10$^+$, Ki-67 40%$^+$, AE1/AE3$^+$) (Fig. 1B, C). No treatment was done after surgical resection.

Unfortunately, multiple tumor masses were found in the bilateral armpits 3 months after surgery. The largest tumor mass was 3 cm $\times$ 2 cm in size in his right armpit. By pathological examination of the dissected bilateral axillary lymph node, 6 in 12 right axillary lymph nodes were melanoma positive, and one of 18 left axillary lymph nodes was melanoma positive. The *NRAS* p.Q61H mutation was detected by next-generation exon sequencing of the tumor mass (Table S1). We also sequenced the patient's family members using blood samples, no *NRAS* mutation was found, indicating the mutation is not inherited (Table S2). Only 2 months later, tumor masses in the armpits were observed again, and a computerized tomography (CT) scan indicated a relapse (Fig. 1D).

Until now, there is a lack of standard recommended guidelines specific to the treatment of CMN. For melanoma patients of all ages who lack *BRAF* mutations, anti-programmed cell death protein 1 (PD-1)-based immune therapy is a first-line treatment according to *NCCN Guidelines Version 2.2021 Melanoma: Cutaneous*. PD-1 inhibition was reported to be effective in a child with congenital pigment-synthesizing metastatic melanoma.[4] Therefore, we tested the effect of pembrolizumab, an anti-PD-1 antibody, in this case. Unfortunately, the lymph nodes in the right armpit became enlarged, and the child's right upper extremity became inflexible after two rounds of pembrolizumab treatment (30 mg every four weeks), indicating this patient was resistant to anti-PD-1-based immunotherapy. Pembrolizumab treatment was

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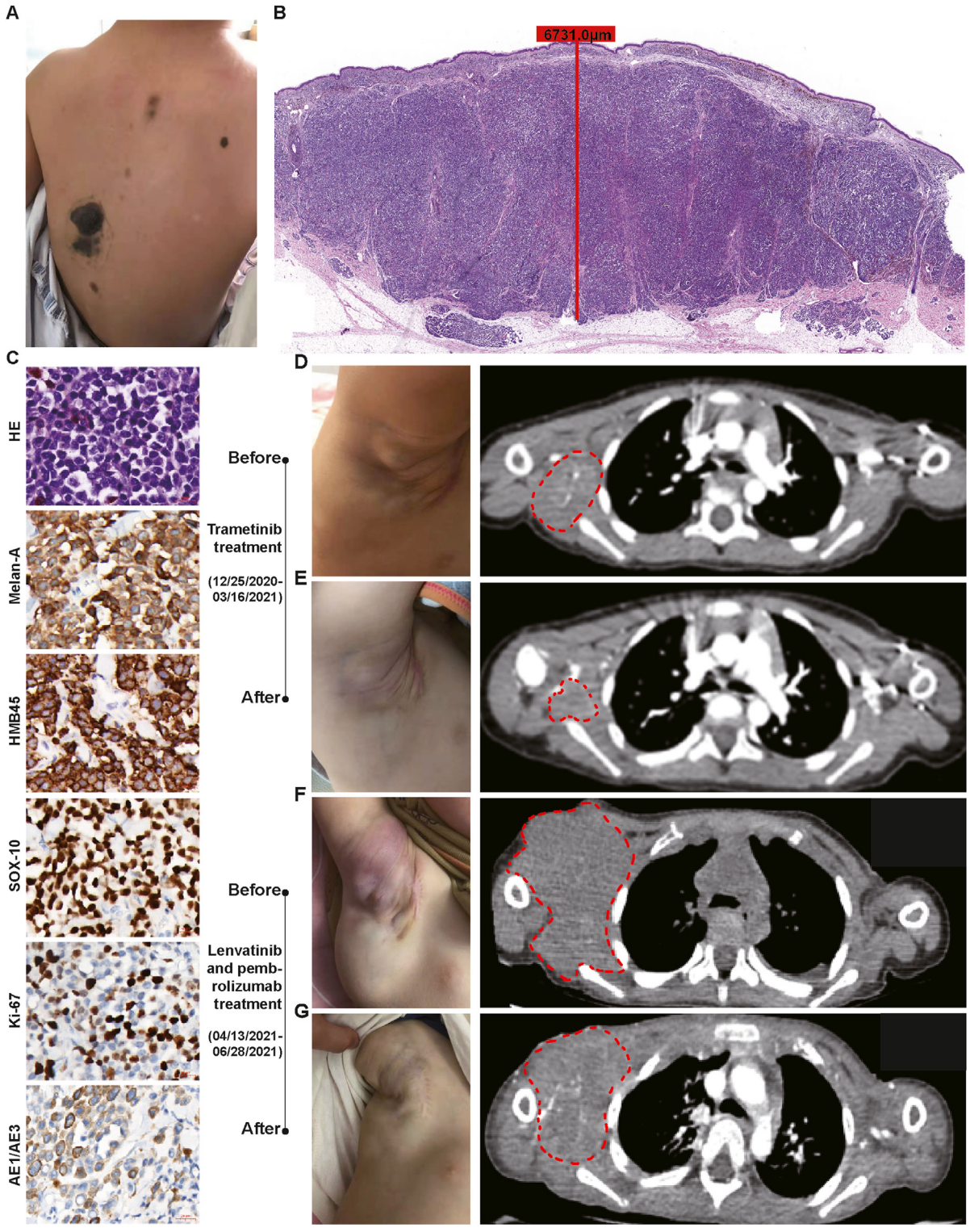

Figure 1 The patient was diagnosed with CMN. Both trametinib and the combination of lenvatinib and pembrolizumab were effective in the CMN patient who was confirmed with progression on PD-(L)1 inhibitor. **(A)** Image of primary tumors with large black plaques on the back. **(B)** Hematoxylin and eosin staining showed the tumor as nodular type (Clark V, Breslow 6.7 mm) with no ulcer on the surface and no tumor involvement at the basal lateral margin. **(C)** Immunohistochemistry staining of melanoma markers on resected tumor tissue. The result showed that Melan-A, HMB45, SOX-10, and AE1/AE3 were positive in almost all cancer cells, and Ki-67 was positive in about 40% of cells. **(D)** Tumors enlarged before trametinib treatment. **(E)** Tumor shrinkage was observed in the armpits after trametinib treatment. **(F, G)** The combination of lenvatinib and pembrolizumab was effective in CMN that was resistant to trametinib. Tumors in the armpits before (F) and after (G) the combination of lenvatinib and pembrolizumab treatment. The tumor edge has been marked in (D—G).

discontinued afterward. Since case studies showed that trametinib, a MEK inhibitor, might be effective on *NRAS*-driven CMN and central nervous system melanoma patients, trametinib (0.02 mg/kg once a day, orally) was given to this patient after full communication with the patient. After 2-weeks trametinib administration, the patient's response was encouraging. First, the tumors in the armpits shrunk significantly (Fig. 1D, E). Second, an obvious improvement in the right upper limb activity and a rapid mood improvement was observed in the child. Third, there was no obvious adverse reaction during the treatment. Response to trametinib treatment lasted for 1.5 months before tumor progression was observed. We then increased the dosage of trametinib to 0.025 mg/kg once a day, but the tumor mass was still slowly growing, and the child's condition worsened. The right axillary lymph nodes were gradually enlarged and new lumps were found under the right scapula, making it difficult for the child to lift the right upper limb, and the child cried frequently. As a result, we stopped trametinib use afterward. In total, the patient was treated with trametinib for 3.5 months.

Since the patient is not qualified for surgery, we then evaluated other drug treatment options. According to the leap-004 study, the combination of lenvatinib, a vascular endothelial growth factor (VEGFR) inhibitor, and pembrolizumab is still effective in patients with advanced melanoma who have confirmed progression on PD-(L)1 inhibitor.[5] Therefore, the treatment of 4 mg of lenvatinib combined with 30 mg of pembrolizumab was used for this patient. One week later, the performance status and appetite of the patient showed great improvement (Fig. 1F, G). There were no obvious adverse reactions during the period. Two months later, the case was reviewed as tumor progression. The patient died a month later. Children with advanced *NRAS*-mutated CMN who have failed first-line therapy have an average overall survival of less than 15 days (Table S3). In this case, the child was treated with trametinib for 87 days, and treated with a combination of lenvatinib and pembrolizumab for 76 days after resistance to trametinib. Both trametinib and the combination of lenvatinib and pembrolizumab significantly prolonged the survival of this child patient.

Based on our case study, trametinib was able to control CMN progression and relieve the patient's symptoms, indicating potential trametinib application as a first-line treatment for CMNs with *NRAS* mutations. The combination of lenvatinib and pembrolizumab also showed a response in this advanced CMN patient who initially was not responsive to PD-(L)1 inhibitor single agent. Since CMNs are very rare, it is difficult to initiate more comprehensive clinical trials to evaluate the response of treatment options. For a better understanding of the therapeutic strategies of CMNs, we reviewed previously reported CMN cases with different genetic backgrounds and treatments (Table S3).

In summary, once CMN is detected or clinically suspected, the routine practice is immediate surgical resection (total excision if possible). The patients who received resection at an early stage were observed to survive without tumor progression for years. For CMN patients who are not applicable for surgical resection, targeted therapy and anti-PD1-based immune therapy are available options. However, pembrolizumab failed to control the disease in our case. If *NRAS* hotspot mutations were found in patients based on biopsy and genetic analysis, MEK inhibitor was used and clinical response was observed in those patients. For patients without *NRAS* mutations, interferon α was reported to be effective. Histone deacetylase inhibitors were proven to induce cell death in large/giant CMNs in a preclinical trial and might be used as an adjunct therapy in CMN patients (Table S3).

Ethics declaration

All procedures were conducted based on the ethics approval obtained from the Independent Ethics Committee of the Third People's Hospital of Zhengzhou (No. 2020-04-006-M0). All patients or their parents gave consent for their photographs and medical information to be published in print and online with the understanding that this information may be publicly available.

Conflict of interests

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2023.05.007.

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