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Primary Malignant Melanoma of the Lung with Unusual ARID1A K1010R Somatic Mutation: Exploring the Highly Variable Genomic Phenotype among Melanomas

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Abstract

Melanoma has the highest prevalence of somatic mutations among all malignancies [1-5]. Primary lung melanoma is rare, representing 0.01% of all primary lung tumors [6-11]. We present a case with no common melanoma-associated mutations but a mutation in the ARID1A K1010R gene, highlighting a novel mutation that may guide future research and therapies.

Introduction

In 2024, it is estimated that 101,000 new cases of cutaneous melanoma will be diagnosed in the United States with approximately 8300 associated fatalities [1]. Staging at diagnosis impacts treatment options and predicted survival length. The 5-year survival rate for localized cutaneous melanoma is 100%, whereas if the melanoma metastasized, the survival rate is reduced to 35% [2]. Genetic mutations such as BRAF and NRAS predispose the development of melanoma. Other contributing factors include chronic UV exposure, which in contrast to genetic susceptibility, is associated with increased amounts of CCND1 and CDK4 oncogenes and the loss of chromosome 10 [3].

Patients with a history of melanoma have a high risk of a second primary cutaneous melanoma diagnosis within the first two years, and this risk remains elevated for at least 20 years [4]. Only 7% of cutaneous melanomas involve the scalp, an area highly susceptible to chronic sun exposure. Scalp melanomas are aggressive, have a high mitotic rate, and higher local recurrence rates compared to other locations due to the thickness of the primary lesion and the anatomic constraints on appro-

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priate excision margins. The 5-year survivorship rates of scalp vs non-scalp melanomas are 44.1% and 62.9% respectively [3]. Here we present a case of a middle-aged male with a history of multiple cutaneous melanomas found to have metastatic melanoma in both lungs.

Case Report

A 63-year-old non-smoking male with a history of multiple melanomas and lifelong career as a steelworker, presented for evaluation of multiple bilateral lung nodules discovered incidentally on a chest radiograph. Four years prior, he was diagnosed with nodular melanoma of the scalp and underwent Mohs surgery for lesion excision. There was recurrent crusting at the surgical site, but biopsy of the area six months postoperatively showed no residual melanoma. Two of his siblings also had a history of melanoma but there was no family history of lung cancer.

CT chest was performed two weeks later (Figure 1), revealing a total of five lung nodules: A nodule in the Right Middle Lobe (RML; 4 mm), two nodules in the Right Lower Lobe (RLL; 11 mm, 4 mm), a nodule of the Left Upper Lobe (LUL; 25mm x19 mm), and a nodule in the Left Lower Lobe (LLL; 19 mm x19 mm). No axillary, mediastinal or hilar lymphadenopathy was noted. An endobronchial ultrasound-guided transbronchial needle aspiration was performed, and pathologic tissue analysis identified metastatic melanoma of the RLL, LUL and LLL (Figure 2). Biopsy of lung station 11L was negative for malignancy. The patient was subsequently referred to oncology and started treatment with nivolumab and relatlimub-rmbw. Cranial MRI showed no evidence of intracranial metastatic disease.

Lung tissue samples were sent for genetic testing. Common mutations associated with melanoma such as BRAF(V600E/V600K) and KIT were not detected. Tests for other cancer-associated genetic alterations including NTRK1/NTRK2/NTRK3 fusion, RET fusion, ALK fusion, ROS-1 fusion, were all undetectable. Next Generation Sequencing (NGS) of cell-free DNA (Guardant 360) detected mutations in ARID1A K1010R (0.4%, variants of uncertain clinical significance). NGS of 88 and 160 genes using cell free RNA showed no significant alterations. The MSI fragment analysis test demonstrated undetermined results. One month after diagnosis, PET-CT scan revealed that several lung nodules had decreased in size compared to prior imaging.

Discussion

Melanoma exhibits the highest prevalence of somatic mutations per base pair of any known malignancy (Figure 3) [5]. The genetic phenotype of primary lung melanoma is not well understood. In the presented case, genetic testing for common oncogenic mutations was unremarkable. ARID1A K1010R, a mutation of unknown significance, was the only genetic mutation identified on the test. This case report serves to add to the growing body of literature further characterizing the highly variable genetic phenotype of melanoma and to provide a potential link between the ARID1A K1010R gene and melanoma.

The patient had significant occupational and past medical history that could have potentiated the development of melanoma. Previous studies have demonstrated that ARID1A mutations tend to occur much later in the progression of melanoma and may have an association with cumulative sun exposure [6]. The patient also had a 35-year history of metalworking, which has known associations with the development of melanoma [7].

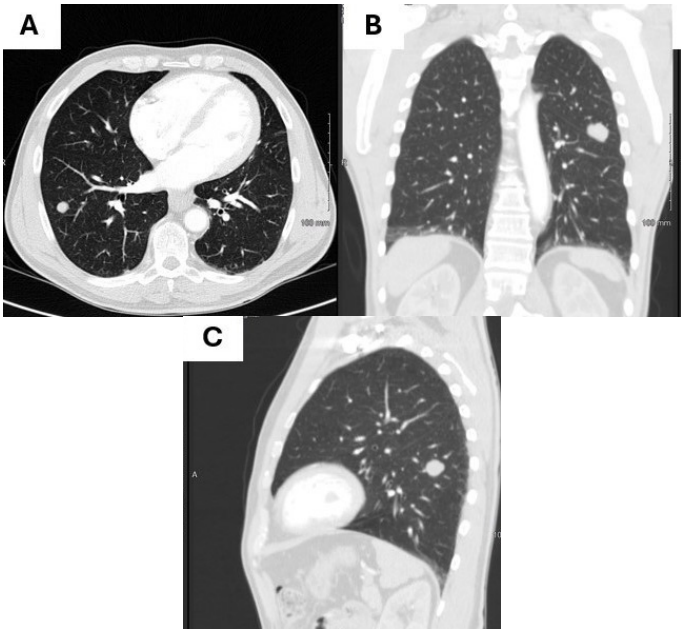

Figure 1: Metastatic melanoma presenting as multiple bilateral noncalcified pulmonary nodules on non-contrast CT imaging. **(A)** axial view; 4mm pulmonary nodule in right middle lobe. **(B)** coronal view; pulmonary nodule (25mm x 19mm) in left upper lobe. **(C)**. sagittal view; 11mm pulmonary nodule in left lower lobe.

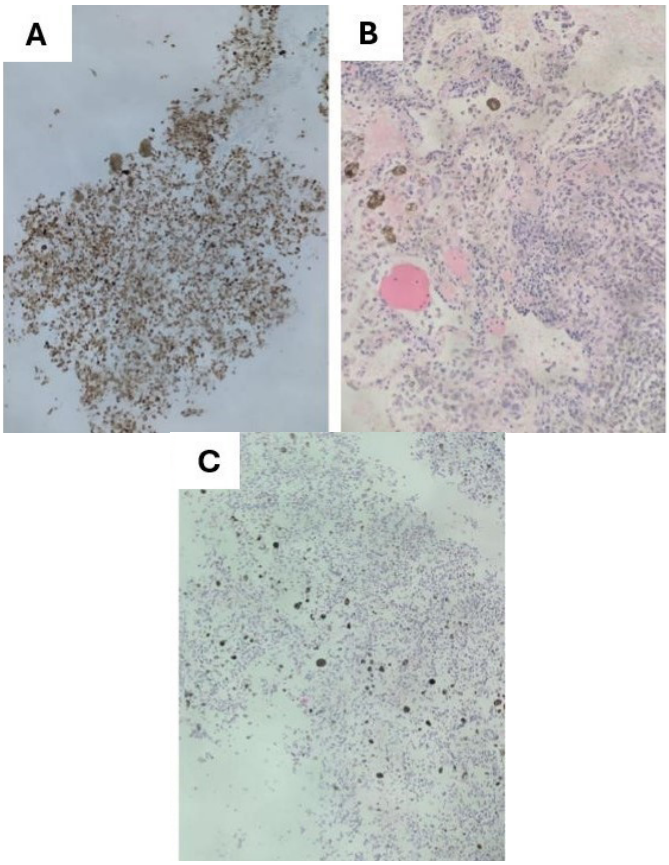

Figure 2: Metastatic melanoma of the lung. **(A)** Immunohistochemical staining of lung tissue for sox10, highlight sheets of malignant melanoma cells. **(B,C)** Hematoxylin and eosin **(H&E)** staining shows pleomorphic malignant cells with pigment.

Further characterization of these genetic phenotypes is essential for the development of more effective targeted therapies. Over a decade ago, patients with metastatic melanoma faced poor clinical outcomes with survival rates of less than 5%. However, recent advances in melanoma treatment including targeted therapies and immunotherapies have dramatically

improved prognosis. Combination immunotherapy now offers a 5-year overall survival rate to nearly 50% of patients, while single-agent PD-1 inhibitors or combination targeted therapies provide survival rates exceeding 33% [8]. Future progress in melanoma treatment will depend on overcoming treatment resistance mechanisms and identifying predictive biomarkers rather than simply expanding on the current standard of care [8].

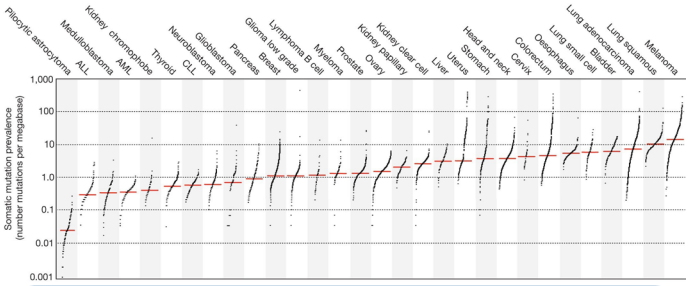

Figure 3: Graph demonstrating the increased prevalence of somatic mutations in melanoma compared to other forms of cancer.

Adapted from "Signatures of mutational processes in human cancer," by Alexandrov, L, 2013, Nature 500, 415–421 (2013). https://doi.org/10.1038/nature12477. Reprinted or adapted with permission.

Melanoma is the sixth most common cause of mortality in the United States [9]. However, primary metastatic melanoma of the lung is relatively rare, and its pathogenesis and optimal treatment strategies are not well characterized. Due to the high somatic mutation rate in melanoma, the condition often responds well to immunotherapy and targeted therapy. The identification of genetic mutations affiliated with melanoma such as BRAF, which is present in up to 66% of cases, has revolutionized treatment options [10]. Targeted therapies against BRAF such as vemurafenib and combination therapies (i.e. debrafenib and trametinib) have significantly improved the prognosis of melanoma by more effectively inhibiting the pathways driving tumor growth.

Historically, metastatic melanoma carried a poor prognosis, but recent advancements in oncologic pharmacotherapy have significantly improved survival rates. While conventional therapies have demonstrated limited efficacy, novel therapeutic approaches including BRAF/MEK inhibitor combination therapies and PD-1 checkpoint immunotherapy have shown promising clinical outcomes. Although ARID1A mutations are not currently well understood, the patient's positive response to combination immunotherapy highlights its potential as a treatment option for melanoma with an ARID1A mutation. 10 years ago, a diagnosis of metastatic melanoma carried a grim prognosis; today, advances in targeted therapies and immunotherapy offer significantly improved outcomes and renewed optimism for patients and clinicians.

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The authors obtained written consent from patients for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

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