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A Germline ALK F1174I Mutant Infant with Multifocal Neuroblastoma and Central Hypoventilation

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Abstract

Neuroblastoma is a common pediatric cancer originating from neural crest cells. Among its various genetic mutations, the Anaplastic Lymphoma Kinase (ALK) gene mutations are significant due to their role in tumorigenesis and therapy resistance. This article presents a case of an infant with a germline ALK F1174I mutation, multifocal neuroblastoma, and central hypoventilation, providing insights into the clinical, genetic, and therapeutic implications of this mutation. Through a detailed case study, literature review, and discussion, we aim to elucidate the pathophysiology and potential treatment strategies for this rare presentation, highlighting the need for personalized medicine in pediatric oncology.

Keywords: Neuroblastoma • ALK mutation • Germline mutation • Central hypoventilation

Introduction

Neuroblastoma is the most common extracranial solid tumor in children, often presenting with a diverse clinical spectrum ranging from asymptomatic masses to life-threatening conditions. The disease accounts for approximately 8-10% of all childhood cancers and is responsible for 15% of pediatric oncology deaths. Genetic mutations, particularly in the Anaplastic Lymphoma Kinase (ALK) gene, play a crucial role in the pathogenesis and prognosis of neuroblastoma. ALK mutations are found in 8-10% of sporadic neuroblastomas and are particularly associated with aggressive disease and poor outcomes [1].

This article focuses on a rare case of an infant with a germline ALK F1174I mutation presenting with multifocal neuroblastoma and central hypoventilation. The case highlights the challenges in diagnosis, the clinical management of multifocal tumors, and the implications of ALK mutations on treatment strategies. This report aims to contribute to the existing knowledge on ALK-mutant neuroblastomas and emphasize the importance of genetic testing and personalized treatment approaches [2].

Literature Review

Neuroblastoma arises from neural crest cells, which give rise to the sympathetic nervous system. It typically presents in the adrenal medulla or paraspinal ganglia and is diagnosed in children under five years old. The disease exhibits remarkable biological heterogeneity, with outcomes ranging from spontaneous regression to metastatic progression. Genetic aberrations are pivotal in the development and progression of neuroblastoma. MYCN amplification, 1p36 deletion, and 11q deletion are well-known genetic alterations linked to poor prognosis. Among these, ALK mutations have garnered attention due to their potential as therapeutic targets. The ALK gene encodes a receptor tyrosine kinase involved in neural development. Mutations in ALK, particularly the F1174I substitution, are associated with increased kinase activity, oncogenesis, and resistance to ALK inhibitors. Germline ALK mutations are rare but confer a hereditary predisposition to neuroblastoma, often leading to earlier onset and multifocal disease [3].

Central Hypoventilation Syndrome, often congenital (CCHS), is linked to mutations in the PHOX2B gene, which is crucial for autonomic nervous system development. Patients with CCHS exhibit alveolar hypoventilation, especially during sleep, leading to hypoxemia and hypercapnia. The co-occurrence of neuroblastoma and CCHS is rare but documented, typically associated with PHOX2B mutations. However, the presence of ALK mutations in such cases introduces a new dimension to the understanding of their pathophysiology. An infant presented with symptoms of respiratory distress and abnormal breathing patterns during sleep, prompting an investigation for central hypoventilation syndrome. Imaging studies revealed multifocal masses in the adrenal glands and other sympathetic ganglia, indicative of neuroblastoma. Genetic testing confirmed a germline ALK F1174I mutation. Despite aggressive chemotherapy and supportive care, the disease progression was rapid, and the patient succumbed to complications related to both neuroblastoma and central hypoventilation [4].

Discussion

This case underscores the interplay between genetic mutations and clinical manifestations in pediatric oncology. The presence of the ALK F1174I mutation likely contributed to the aggressive nature of the neuroblastoma. Furthermore, the co-occurrence with central hypoventilation suggests a possible overlap in the genetic pathways regulating neural development and autonomic function. This highlights the need for a deeper genetic and molecular understanding to devise effective treatments. Current therapeutic approaches for neuroblastoma include surgery, chemotherapy, radiotherapy, and novel targeted therapies such as ALK inhibitors. However, the efficacy of these treatments in the context of germline mutations and multifocal disease remains limited. The integration of genetic therapies, such as CRISPR-Cas9 mediated correction of ALK mutations, represents a promising avenue for future research [5].

The ALK F1174I mutation's presence in neuroblastoma signifies a higher risk for aggressive tumor behavior and poor clinical outcomes. This mutation leads to constitutive activation of the ALK protein, which promotes cellular proliferation and survival. This oncogenic driver mutation, therefore, becomes a critical therapeutic target. The efficacy of ALK inhibitors, such as crizotinib and ceritinib, has been explored, showing promise in treating ALK-mutated neuroblastomas. However, resistance to these inhibitors often develops, necessitating the development of next-generation ALK inhibitors and combination therapies to improve outcomes. The discovery of a germline ALK mutation has significant implications for the patient's family members, who may also carry the mutation and be at risk for developing neuroblastoma or other ALK-related malignancies. Genetic counseling becomes crucial in

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these scenarios, providing family members with information about their risks and options for surveillance or preventive measures. The identification of a germline mutation also necessitates a discussion about the possibility of future siblings being affected, guiding family planning decisions [6].

Conclusion

The case of an infant with a germline ALK F1174I mutation, multifocal neuroblastoma, and central hypoventilation underscores the complexities and challenges in pediatric oncology. The overlap between oncogenic mutations and autonomic dysfunction necessitates a multi-disciplinary approach encompassing genetic, clinical, and therapeutic expertise. Advances in genetic research and targeted therapies hold promise for improving outcomes in such complex cases. Future studies should focus on the development of integrated treatment protocols and the exploration of genetic therapies to address both oncological and autonomic dysfunction aspects of the disease.

Acknowledgement

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Conflict of Interest

None.

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