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Rosai-Dorfman-Destombes Disease: A Clonal Histiocytic Neoplasm

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Abstract

Rosai-Dorfman-Destombes disease (RDD) has long been identified as a non-clonal histiocytic proliferation presenting with bulky lymphadenopathy. The recent decade has shown a significant paradigm shift in understanding the pathophysiology of histiocytic neoplasia. Mutations in genes causing constitutive activation of the MAPK/ERK pathway in nearly half of RDD cases have highlighted its clonal origin. Also, the knowledge of the pathway has led to the utilization of targeted therapy including MEK inhibitor cobimetinib in the management of refractory cases. We provide a brief review of the genetic analysis of sporadic RDD highlighting the utility of molecular analysis in clinical practice.

Keywords: Histiocytic Proliferation; Rosai Dorfman Destombes Disease; Sinus Histiocytosis with massive Lymphadenopathy; Clonal; MAPK/ERK; BRAF; MEK Inhibitor Cobimetinib

Introduction

Rosai-Dorfman-Destombes disease (RDD) also known as sinus histiocytosis with massive lymphadenopathy is a rare histiocytic proliferation mostly presenting in children and young adults with massive bilateral cervical lymphadenopathy and constitutional symptoms including fever, weight loss, and night sweats [1]. Histologically the lymph nodes show sinusoidal infiltration by a histiocytic proliferation with emperipolesis. The histiocytes characteristically show vesicular chromatin and conspicuous nucleolus. While immunostaining is not required for diagnosis, it certainly useful for the exclusion of morphological mimics, and in challenging cases with atypical morphology. The histiocytes express CD68 and CD163 and characteristically express S-100 with the absence of CD1a, and langerin. Extranodal involvement may be seen in skin [2,3]. Retro-orbital tissue and CNS [4]. Cases with an aggressive clinical presentation are well known. Also, RDD has recently been described in the "R group" based on the reclassification in 2016 [5].

While originally considered as a non-neoplastic condition, the indications towards a clonal nature were evident with early clinical reports showing concomitant occurrence of RDD with LCH indicative of activation of a common genetic pathway [6]. Similarly, a recent case report of mixed histiocytosis showed a common genetic defect of MAP2K1-driven mixed histiocytosis with Langerhans cell histiocytosis, Rosai-Dorfman-Destombes disease, and Erdheim-Chester disease feature, and a clonally-related acute myeloid leukemia.

Subsequently, mutually exclusive *MAP2K1* and *KRAS* mutations were found in 33% of RDD cases, by targeted massively parallel sequencing, indicative of MAPK/ERK pathway activation. Of interest, all cases with mutations had multifocal disease compared to only 27% cases without mutation in that study [7]. More recently a study identified kinase mutations involving *KRAS* (4 cases), *MAP2K1* (2 cases), *NRAS*, *ARAF*, and *CSF1R* by whole exome and whole transcriptome sequencing of 17 RDD cases highlighting

clonal origin in nearly half of the cohort of RDD. Also, alterations in genes involved in DNA mismatch repair (*ERCC2*, *LATS2*, *BRCA1*, *ATM*), intracellular trafficking (*SNX24*), transcriptional regulation (*CIC*, *SFR1*, *BRD4*, *INTS2*, *PHOX2B*), cell cycle regulation (*MUC4*, *PDS5A*), and the ubiquitin-proteasome pathway (*USP35*) was reported [8]. While *BRAF* mutations have been more commonly reported in LCH [9] and Erdhiem Chester disease [10] only a few recent case reports have reported *BRAF* mutations in RDD [11-13]. Of interest, one of these cases with a *BRAF* V600E mutation presented with isolated lymphadenopathy and subsequently underwent spontaneous resolution [13]. While the other two cases presented with a more aggressive clinical outcome, one RDD with mutant exon 12 of *BRAF* and another case of mixed histiocytosis (RDD+ Langerhans cells histiocytosis) with *BRAF* V600E had CNS involvement [11,12]. A recent case report described *NRAS* 117S mutation in a case of RDD presenting in an elderly gentleman with atypical aggressive morphology and aggressive clinical manifestations. RDD presented as an abdominal wall mass, abdominal lymphadenopathy, and with mass-like lesions involving liver and lung and subsequently skin lesions. Microscopically the histiocytic cells showed large hyperchromatic nuclei with prominent nucleoli and high mitotic activity along with prominent emperipolesis. The disease showed partial radiological response on treatment with MEK inhibitor cobimetinib [14].

The role of MAPK/ERK pathway activation in the development of RDD was further exemplified by a multicentric study describing 12 cases of composite B-cell lymphoma with focal RDD [6]. The B-cell lymphomas were most commonly nodular lymphocyte predominant Hodgkin lymphoma and classic Hodgkin lymphoma (involved in ~80% cases), and rarely small lymphocytic lymphoma and marginal zone lymphoma. The RDD presented as histiocytes showing emperipolesis and expression of S-100. Of interest, in most all (~86%) cases, areas with RDD showed activation of the MAPK/ERK pathway as evidenced by overexpression of p-ERK. These findings are concordant to other studies showing p-ERK overexpression in RDD cases with MAP2K1 mutation [7-15]. Interestingly, all the cases in this series were negative for gene mutations especially involving the MAPK/ERK pathway, despite overexpression of p-ERK. This may be indicative of secondary activation of MAPK/ERK pathway from the autocrine and paracrine effect of factors produced by the neighboring lymphoma inducing RDD type phenotype [7]. Similarly, the expression of CyclinD1 in a subset of cases of RDD also lends support towards the activation of MAPK/ERK pathway, as has been described previously in other neoplasia like Langerhans cell histiocytosis [16].

In conclusion, while the current WHO classification of hematopoietic tumors does not include RDD as a histiocytic neoplasm, recurrent genetic alterations especially those causing activation of the MAPK/ERK pathway promote for the inclusion of Rosai-Dorfman-Destombes disease as a clonal histiocytic disorder. Secondly, molecular analysis for RDD is not routine clinical practice for all cases in most institutions, especially in developing countries. However, paraffin-embedded formalin-fixed tissue may be used, if required, for massively parallel sequencing (next generation targeted sequencing) to identify genetic alterations in the RAS-RAF-ERK pathway for targeted treatment, especially with MEK inhibitor cobimetinib, specifically in cases with refractory and aggressive clinical course [17,18].

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