Rosai–Dorfman Disease Harboring an Activating KRAS K117N Missense Mutation

Vignesh Shanmugam¹ · Elizabeth Margolskee² · Michael Kluk² ·
Tamara Giorgadze² · Attilio Orazi²

Received: 2 January 2016 / Accepted: 24 February 2016 / Published online: 27 February 2016
© Springer Science+Business Media New York 2016

Abstract Rosai–Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy is a rare histiocytic proliferation that is generally considered to be reactive with a benign clinical course. The etiology of RDD is very poorly understood. Recent studies have shown frequent BRAF, NRAS, KRAS, and PIK3CA activating mutations in several histiocytic neoplasms highlighting the emerging importance of the RAF/MEK/ERK pathway in the pathogenesis of these diseases. Here we report a case of Rosai–Dorfman disease involving the submandibular salivary gland with a KRAS K117N missense mutation discovered by next-generation sequencing. These results suggest that at least a subset of RDD cases may be clonal processes. Further mutational studies on this rare histiocytic disease should be undertaken to better characterize its pathogenesis as well as open up potential avenues for therapy.

Keywords Histiocytosis · Rosai–Dorfman disease · Next generation sequencing · Sinus histiocytosis with massive lymphadenopathy · Clonality · Pathogenesis

Introduction

Histiocytic disorders can broadly be divided into Langerhans cell histiocytoses (LCH) and the non-Langerhans cell histiocytoses. LCH are characterized by typical immunophenotypic (CD1a+/Langerin+/S100+) and ultrastructural findings (Birbeck granules) [1]. The non-LCH are a heterogeneous group of disorders that do not meet the phenotypic criteria for LCH. Juvenile xanthogranuloma (JXG) is the most common of the non-LCH [2], which is a benign proliferative disorder of children typically characterized by the presence of “Touton” giant cells and a distinct immunophenotype (factor XIIIa +/CD68 +/CD14 +/CD1a-/S100-). The majority of the other non-LCH share the histopathological findings of JXG with the exception of Rosai–Dorfman disease (RDD) and multicentric reticulohistiocytosis [2].

RDD or sinus histiocytosis with massive lymphadenopathy (SHML) is a rare histiocytic proliferation that is generally considered to be reactive with a benign clinical course [1, 3, 4]. It typically presents with bilateral cervical lymphadenopathy although extranodal presentations are common (40 % of cases) [1]. Effacement of tissue architecture with CD68+/S100+ macrophages displaying emperipolesis is diagnostic. The etiology of RDD is very poorly understood. Recent studies have shown frequent BRAF V600E mutations in Langerhans cell histiocytosis (LCH) [5, 6], Erdheim–Chester disease (ECD) [7], histiocytic sarcoma [8], and follicular dendritic cell sarcoma [8]. Further, NRAS, KRAS, and PIK3CA activating mutations have also been shown in ECD [6, 9], highlighting the emerging importance of the RAF/MEK/ERK pathway in some histiocytic disorders.

Here we report a case of RDD involving the submandibular salivary gland with a KRAS K117N missense mutation discovered by next-generation sequencing.

✉ Vignesh Shanmugam
vis2018@qatar-med.cornell.edu

¹ Department of Pathology and Laboratory Medicine, Weill Cornell Medicine – Qatar, Education City,
PO Box 24144, Doha, Qatar

² Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, 1300 York Avenue, New York, NY 10065, USA

Case Report

The patient is a 45-year-old Canadian man with a past medical history of diabetes mellitus who presented with a two-year history of bilateral neck swelling and fatigue. An excisional biopsy of the left submandibular salivary gland was performed and a diagnosis of RDD was rendered at the outside hospital. A CT scan showed extensive bilateral neck adenopathy as well as mild, diffuse prominence of tissues within the roof of the nasopharynx. Furthermore, imaging of the thorax showed left axillary and mediastinal lymphadenopathy. He subsequently presented to our institution (1 year after symptom onset) for consultation. Additional history revealed recent weight loss, night sweats, and fatigue. Physical exam showed bilateral palpable cervical lymphadenopathy but was otherwise unremarkable. Basic laboratory investigations including complete blood counts, electrolytes, renal and liver function tests and inflammatory markers (ESR and CRP) were unremarkable.

Microscopic examination of the submitted slides from the left submandibular gland showed effacement and infiltration of the normal lobular architecture of the salivary gland by a diffuse syncytial proliferation of voluminous histiocytic cells with foamy cytoplasm, and round vesicular nuclei with prominent nucleoli (Fig. 1a, b). Frequent emperipolesis was seen (Fig. 1c). Rare multinucleated “Touton” type giant cells were also seen (Fig. 1d). There were also scattered lymphocytes, plasma cells, and eosinophils. No mitotic figures were seen. The uninvolved salivary gland was unremarkable. No subcapsular sinuses were identified in all sections of the nodule suggesting true extranodal involvement and not periglandular lymph node involvement.

Immunohistochemistry showed that the histiocytic cells were positive for S100, CD68, CD163, and factor XIIIa (Fig. 1e–g). They were negative for CD1a, langerin, CD30, cytokeratin, and calponin. The plasma cells were demonstrated to be polytypic for kappa and lambda light chains by in situ hybridization. In situ hybridization for Epstein Barr virus RNA was negative. These findings were diagnostic of RDD. Given the unusual finding of Touton-type giant cells and the occasional presence of factor XIII positive macrophages, other non-LCH were also considered in the differential diagnosis, including ECD. However, the clinical picture and imaging studies showed no evidence of bone lesions or other involvement suspicious for ECD. To further evaluate this patient, we performed a targeted next generation sequencing panel (Ion AmpliSeq™ Cancer Hotspot Panel v2, ThermoFisher Scientific). This revealed a KRAS K117N (COSM19940) missense variant. The tumor cellularity of the analyzed sample was

approximately 60 %. The allele frequency of the KRAS mutation was 11 % (70/668 reads). The presence of this variant was confirmed upon repeat testing. No BRAF V600 mutation was identified.

After the diagnosis of asymptomatic RDD was established, the patient did not receive any treatment and was closely followed up. Serial clinical exams and imaging did not show additional findings up to 1 year after symptom onset.

Discussion

Extranodal RDD involvement most commonly involves anatomically sensitive regions of the head and neck areas, especially the orbit, nasal cavity, and paranasal sinuses [10, 11]. The major salivary glands are also a common site of involvement [10, 11] with about 15 cases of salivary gland RDD reported in the English literature thus far. Most of the reported cases showed parotid and submandibular gland involvement [10–16]. In addition, RDD may also involve the upper respiratory tract, thyroid, and central nervous system and rarely the gastrointestinal system [17]. Demonstration of potentially actionable mutational patterns on biopsy may create a role for targeted neoadjuvant therapies in the management of surgically challenging lesions.

Classical RDD is characterized by replacement of tissue architecture by histiocytes, lymphocytes, and plasma cells, which may simulate the appearance of lymph node sinuses. Emperipolesis is a classic finding in RDD, which distinguishes it from the other histiocytoses. RDD histiocytes express S100 in addition to histiocytic markers CD68 and CD163 and are negative for CD1a and factor XIIIa [17]. The presence of “Touton” giant cells and foamy Factor XIIIa-positive histiocytes in this case broadened the differential diagnosis to include other histiocytoses like ECD and JXG. However, the absence of sclerotic long bone disease on imaging studies and other typical clinical symptoms like bone pain essentially excluded this possibility [18]. The compelling clinical, morphological, and immunohistochemical findings favored a final diagnosis of RDD.

The presence of Touton giant cells and foamy histiocytes, albeit uncommon, has been previously observed in cutaneous RDD [19]. However, to the best of our knowledge, this feature has not been reported previously in an extracutaneous site. Morphological associations between LCH and non-LCH have been demonstrated in several case reports. Co-existence of RDD and LCH in the same patient and often in the same lesion is well documented in the literature [20–23]. The co-occurrence of ECD and LCH has

Fig. 1 **a** Low power ($\times 2$) and **b** high power ($\times 20$) Hematoxylin and Eosin (H&E) image showing the histiocytic proliferation with infiltration of normal adjacent lobular architecture of salivary gland; *inset* high magnification ($\times 100$) image showing nuclear detail of

histiocytes; **c** shows an example of emperipolesis; **d** multinucleated “Touton” type giant cells; the histiocytes were immunoreactive for **e** S100, **f** CD68, and **g** FXIIIa

also been reported [24]. The common origin of macrophages and dendritic cells (DC) from a common macrophage-DC progenitor has been established in the literature [2]. It is tempting to think that there may be precursor cells capable of transdifferentiation and maturation towards either lineage in these lesions.

Historically, RDD is considered non-clonal and reactive [3, 4]. However, RDD lesions have been reported to undergo malignant transformation to histiocytic sarcoma [25, 26] and high-grade lymphoma [27] indicating their potential for genomic instability. In this case, we identified a low allele frequency KRAS variant consistent with a subclonal mutation. Given that a cancer hotspot panel was used for testing, it is possible that other mutations could be present which were not detectable with the assay used. The presence of low-level somatic mutations in various genes is becoming increasingly interpreted in some clinical contexts [28–30] to indicate the presence of an underlying clonal population in the tissue tested; however, the presence of such mutations and/or clonal populations is not necessarily diagnostic of malignancy and may be of uncertain prognostic significance. In each case, the molecular findings must be interpreted in the context of the other clinical and pathologic findings. Further study is required in order to

improve our understanding in these areas, particularly in the context of the mutations being recently reported in the literature in a variety of histiocytic disorders.

Little is known about the molecular landscape in histiocytic tumors, possibly due the relative rarity of these lesions as well as their tendency to follow an indolent course. However, recent studies have highlighted the role of the RAS/RAF/ERK (MAPK) pathway in the pathogenesis of several histiocytic disorders, although few cases of RDD have been evaluated [5–9, 31]. The RAS/RAF/ERK (MAPK) pathway is involved in various cellular functions including cellular proliferation, differentiation, and migration; mutation of genes involved in this pathway has been implicated in oncogenesis [32]. The arrival of MEK and RAF inhibitors, such as Trametinib and Vemurafenib, has raised the possibility of new options for the treatment of these diseases [33].

Table 1 summarizes a literature review of gene mutations described in non-LCH, demonstrating the clear preponderance of kinase activating mutations involving the MAPK pathway. In particular, very recently, a study used whole-exome sequencing, RNA-seq, and targeted sequencing techniques to describe several recurrent gene mutations and fusions in LCH and non-LCH (including

Table 1 Literature review of gene mutations described in non-LCH

Category	Gene mutations demonstrated in literature
Erdheim–Chester disease (ECD)	BRAF (p.V600E) [7–9] PIK3CA (p.E542K, p.E545K, p.A1046T, and p.H1047R) [7, 34] NRAS (p.G12D, p.Q61K, p.Q61R) [7, 34] KRAS (p.G12S) [34] MAP2K1 (p.K57E/N, p.Q56P, p.F68L, p.S123T/P, p.E144K, p.E51_Q58del, p.Q58_E62del, p.E102_I103del) [34] ARAF (p.S214A, p.A225 V, p.P539H) [34] BRAF fusions (RNF11-BRAF, CLIP2-BRAF) [34] KIF5B-ALK fusion [34] LMNA-NTRK fusion [34]
Rosai–Dorfman disease (RDD)	NRAS (p.Q61R) [34] KRAS (p.G12D) [34] SMAD4 (p.T521I) [40] MAP2K1 (p.V60M, p.D65M) [34] ARAF (p.N217K) [34]
Juvenile xanthogranuloma (JXG)	NRAS (p.Q61R) [34] KRAS (p.G12D) [34] MAP2K1 (p.T28I, p.L37P, p.E120Q, p.Y130C) [34] ARAF (p.N217K, p.F351L) [34]
Histiocytic sarcoma	BRAF (p.V600E) [8] PTEN deletion (deletion involving exon 7 (c.635-7_639del) [37], exon 6-9 [41] and all 9 exons [41]) t(14;18)—IGH/BCL2 fusion [42]
Langerhans cell sarcoma	BRAF (p.V600E) [8]
Follicular dendritic cell sarcoma	BRAF (p.V600E) [8]

RDD) [34]. Interestingly, that study also found mean variant allele frequencies at levels similar to our study, including a KRAS G12D missense variant in RDD. These very recent findings, in addition to our own, challenge the historical notion that RDD is a purely non-clonal, reactive process [1, 3, 4].

This case is, to the best of our knowledge, the first report of a KRAS K117N missense variant in RDD. This variant has been previously reported in the COSMIC mutational database in other tumor types (colorectal cancer, esophageal adenocarcinoma, myelodysplastic syndrome) [35–37]. In vitro studies suggest this variant allele activates the RAS/RAF/ERK signaling cascade, leading to cell proliferation and vemurafenib resistance [38, 39].

In summary, here we present a case of RDD involving the salivary gland harboring an activating KRAS mutation, suggesting that at least a subset of RDD cases may be clonal processes, which is also consistent with the findings from other recently published work by other authors [31]. Further mutational studies on this rare histiocytic disease should be undertaken to better characterize its pathogenesis as well as open up potential avenues for therapy.

Acknowledgments The authors gratefully acknowledge the contributions of all the staff of the Molecular Pathology Laboratory of New York Presbyterian Hospital/Weill Cornell Medicine in specimen processing and data collection. No major sources of funding.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics Approval For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Swerdlow SH. WHO classification of tumours of haematopoietic and lymphoid tissues. Geneva: World Health Organization; 2008.
2. Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. *Pediatr Blood Cancer*. 2005; 45(3):256–64. doi:10.1002/pbc2246.
3. Paulli M, Bergamaschi G, Tonon L, et al. Evidence for a polyclonal nature of the cell infiltrate in sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease). *Br J Haematol*. 1995;91(2):415–8.

4. Middel P, Hemmerlein B, Fayyazi A, Kaboth U, Radzun HJ. Sinus histiocytosis with massive lymphadenopathy: evidence for its relationship to macrophages and for a cytokine-related disorder. *Histopathology*. 1999;35(6):525–33.
5. Badalian-Very G, Vergilio J-A, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood*. 2010;116(11):1919–23. doi:[10.1182/blood-2010-04-279083](https://doi.org/10.1182/blood-2010-04-279083).
6. Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood*. 2014;124(19):3007–15. doi:[10.1182/blood-2014-05-577825](https://doi.org/10.1182/blood-2014-05-577825).
7. Emile J-F, Diamond EL, Hélias-Rodziewicz Z, et al. Recurrent RAS and PIK3CA mutations in Erdheim–Chester disease. *Blood*. 2014;124(19):3016–9. doi:[10.1182/blood-2014-04-570937](https://doi.org/10.1182/blood-2014-04-570937).
8. Go H, Jeon YK, Huh J, et al. Frequent detection of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. *Histopathology*. 2014;65(2):261–72. doi:[10.1111/his.12416](https://doi.org/10.1111/his.12416).
9. Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim–Chester disease but not in other non-Langerhans cell histiocytoses. *Blood*. 2012;120(13):2700–3. doi:[10.1182/blood-2012-05-430140](https://doi.org/10.1182/blood-2012-05-430140).
10. Goodnight JW, Wang MB, Sercarz JA, Fu YS. Extranodal Rosai–Dorfman disease of the head and neck. *Laryngoscope*. 1996;106(3 Pt 1):253–6.
11. Güven G, Ilgan S, Altun C, Gerek M, Gunhan O. Rosai Dorfman disease of the parotid and submandibular glands: salivary gland scintigraphy and oral findings in two siblings. *Dentomaxillofac Radiol*. 2007;36(7):428–33. doi:[10.1259/dmfr/39858276](https://doi.org/10.1259/dmfr/39858276).
12. Hyman DM, Diamond EL, Vibat CRT, et al. Prospective blinded study of BRAFV600E mutation detection in cell-free DNA of patients with systemic histiocytic disorders. *Cancer Discov*. 2015;5(1):64–71. doi:[10.1158/2159-8290.CD-14-0742](https://doi.org/10.1158/2159-8290.CD-14-0742).
13. Chen T-D, Lee L. Rosai–Dorfman disease presenting in the parotid gland with features of IgG4-related sclerosing disease. *Arch Otolaryngol Head Neck Surg*. 2011;137(7):705–8. doi:[10.1001/archoto.2011.52](https://doi.org/10.1001/archoto.2011.52).
14. Dahlgren M, Smetherman DH, Wang J, Corsetti RL. Rosai–Dorfman disease of the breast and parotid gland. *J La State Med Soc*. 2008;160(1):35–8.
15. Juskevicius R, Finley JL. Rosai–Dorfman disease of the parotid gland: cytologic and histopathologic findings with immunohistochemical correlation. *Arch Pathol Lab Med*. 2001;125(10):1348–50. doi:[10.1043/0003-9985\(2001\)125<1348:RDDOTP>2.0.CO;2](https://doi.org/10.1043/0003-9985(2001)125<1348:RDDOTP>2.0.CO;2).
16. Norman L, Bateman AC, Watters GW, Singh V, Spedding AV. Rosai–Dorfman disease presenting as a parotid mass. *J Laryngol Otol*. 1997;111(11):1091–3.
17. Dalia S, Sagatys E, Sokol L, Kubal T. Rosai–Dorfman disease: tumor biology, clinical features, pathology, and treatment. *Cancer Control*. 2014;21(4):322–7.
18. Dion E, Graef C, Miquel A, et al. Bone involvement in Erdheim–Chester disease: imaging findings including periostitis and partial epiphyseal involvement. *Radiology*. 2006;238(2):632–9. doi:[10.1148/radiol.2382041525](https://doi.org/10.1148/radiol.2382041525).
19. Thawerani H, Sanchez RL, Rosai J, Dorfman RF. The cutaneous manifestations of sinus histiocytosis with massive lymphadenopathy. *Arch Dermatol*. 1978;114(2):191–7.
20. Cohen-Barak E, Rozenman D, Schafer J, et al. An unusual co-occurrence of Langerhans cell histiocytosis and Rosai–Dorfman disease: report of a case and review of the literature. *Int J Dermatol*. 2014;53(5):558–63. doi:[10.1111/ijd.12051](https://doi.org/10.1111/ijd.12051).
21. O'Malley DP, Duong A, Barry TS, et al. Co-occurrence of Langerhans cell histiocytosis and Rosai–Dorfman disease: possible relationship of two histiocytic disorders in rare cases. *Mod Pathol*. 2010;23(12):1616–23. doi:[10.1038/modpathol.2010.157](https://doi.org/10.1038/modpathol.2010.157).
22. Sachdev R, Shyama J. Co-existent Langerhans cell histiocytosis and Rosai–Dorfman disease: a diagnostic rarity. *Cytopathology*. 2008;19(1):55–8. doi:[10.1111/j.1365-2303.2006.00428.x](https://doi.org/10.1111/j.1365-2303.2006.00428.x).
23. Wang K-H, Cheng C-J, Hu C-H, Lee W-R. Coexistence of localized Langerhans cell histiocytosis and cutaneous Rosai–Dorfman disease. *Br J Dermatol*. 2002;147(4):770–4.
24. Pineles SL, Liu GT, Acebes X, et al. Presence of Erdheim–Chester disease and Langerhans cell histiocytosis in the same patient: a report of 2 cases. *J Neuroophthalmol*. 2011;31(3):217–23. doi:[10.1097/WNO.0b013e31820a204e](https://doi.org/10.1097/WNO.0b013e31820a204e).
25. Venkataraman G, McClain KL, Pittaluga S, Rao VK, Jaffe ES. Development of disseminated histiocytic sarcoma in a patient with autoimmune lymphoproliferative syndrome and associated Rosai–Dorfman disease. *Am J Surg Pathol*. 2010;34(4):589–94. doi:[10.1097/PAS.0b013e3181d5dd8f](https://doi.org/10.1097/PAS.0b013e3181d5dd8f).
26. Agarwal A, Pathak S, Gujral S. Sinus histiocytosis with massive lymphadenopathy—a review of seven cases. *Indian J Pathol Microbiol*. 2006;49(4):509–15.
27. Krzemieniecki K, Pawlicki M, Margańska K, Parczewska J. The Rosai–Dorfman syndrome in a 17-year-old woman with transformation into high-grade lymphoma. A rare disease presentation. *Ann Oncol*. 1996;7(9):977.
28. Zaletel K, Gaberšček S. Hashimoto's thyroiditis: from genes to the disease. *Curr Genomics*. 2011;12(8):576–88. doi:[10.2174/138920211798120763](https://doi.org/10.2174/138920211798120763).
29. Kim KH, Suh KS, Kang DW, Kang DY. Mutations of the BRAF gene in papillary thyroid carcinoma and in Hashimoto's thyroiditis. *Pathol Int*. 2005;55(9):540–5.
30. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, Lindsley RC, Mermel CH, Burt N, Chavez A, Higgins JM, Moltchanov V, Kuo FC, Kluk MJ, Henderson B, Kinnunen L, Koistinen HA, Ladvall C, Getz G, Correa A, Banahan BF, Gabriel S, Kathiresan S, Stringham HM, McCarthy MI, Boehnke M, Tuomilehto J, Haiman C, Groop L, Atzmon G, Wilson JG, Neuberger D, Altshuler D, Ebert BL. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488–98. doi:[10.1056/NEJMoa1408617](https://doi.org/10.1056/NEJMoa1408617) (**Epub 2014 Nov 26**).
31. Nelson DS, van Halteren A, Quispel WT, et al. MAP2K1 and MAP3K1 mutations in Langerhans cell histiocytosis. *Genes Chromosomes Cancer*. 2015;54(6):361–8. doi:[10.1002/gcc.22247](https://doi.org/10.1002/gcc.22247).
32. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. *Oncogene*. 2007;26(22):3279–90. doi:[10.1038/sj.onc.1210421](https://doi.org/10.1038/sj.onc.1210421).
33. Zhao Y, Adjei AA. The clinical development of MEK inhibitors. *Nat Rev Clin Oncol*. 2014;11(7):385–400. doi:[10.1038/nrclinonc.2014.83](https://doi.org/10.1038/nrclinonc.2014.83).
34. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. *Cancer Discov*. 2015;. doi:[10.1158/2159-8290.CD-15-0913](https://doi.org/10.1158/2159-8290.CD-15-0913).
35. Smith G, Bounds R, Wolf H, Steele RJC, Carey FA, Wolf CR. Activating K-Ras mutations outwith “hotspot” codons in sporadic colorectal tumours—implications for personalised cancer medicine. *Br J Cancer*. 2010;102(4):693–703. doi:[10.1038/sj.bjc.6605534](https://doi.org/10.1038/sj.bjc.6605534).
36. Dulak AM, Stojanov P, Peng S, et al. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nat Genet*. 2013;45(5):478–86. doi:[10.1038/ng.2591](https://doi.org/10.1038/ng.2591).
37. Papaemmanuil E, Gerstung M, Maltcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood*. 2013;122(22):3616–27. doi:[10.1182/blood-2013-08-518886](https://doi.org/10.1182/blood-2013-08-518886) (**quiz 3699**).
38. Stolze B, Reinhart S, Bullinger L, Fröhling S, Scholl C. Comparative analysis of KRAS codon 12, 13, 18, 61, and 117

- mutations using human MCF10A isogenic cell lines. *Sci Rep*. 2015;5:8535. doi:[10.1038/srep08535](https://doi.org/10.1038/srep08535).
39. Su F, Bradley WD, Wang Q, et al. Resistance to selective BRAF inhibition can be mediated by modest upstream pathway activation. *Cancer Res*. 2012;72(4):969–78. doi:[10.1158/0008-5472.CAN-11-1875](https://doi.org/10.1158/0008-5472.CAN-11-1875).
40. Gatalica Z, Bilalovic N, Palazzo JP, et al. Disseminated histiocytoses biomarkers beyond BRAFV600E: frequent expression of PD-L1. *Oncotarget*. 2015;6(23):19819–25.
41. Carrasco DR, Fenton T, Sukhdeo K, et al. The PTEN and INK4A/ARF tumor suppressors maintain myelolymphoid homeostasis and cooperate to constrain histiocytic sarcoma development in humans. *Cancer Cell*. 2006;9(5):379–90. doi:[10.1016/j.ccr.2006.03.028](https://doi.org/10.1016/j.ccr.2006.03.028).
42. Hayase E, Kurosawa M, Yonezumi M, Suzuki S, Suzuki H. Aggressive sporadic histiocytic sarcoma with immunoglobulin heavy chain gene rearrangement and t(14;18). *Int J Hematol*. 2010;92(4):659–63. doi:[10.1007/s12185-010-0704-8](https://doi.org/10.1007/s12185-010-0704-8).