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Case report

Testicular Rosai-Dorfman disease clonally related to CMML – Case report and literature review

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ABSTRACT

Background: Rosai-Dorfman disease (RDD), a rare form of non-Langerhans cell histiocytosis with heterogenous clinical features, arises from precursor cells that give rise to cells of the histiocytic and monocytic lineages. An association with hematological neoplasms has been reported. Testicular RDD is rarely described, with only 9 reported cases in the literature. Genetic data to assess clonal relationships between RDD and other hematological neoplasms remain scarce. We describe an instance of testicular RDD against a background of chronic myelomonocytic leukemia (CMML), with genetic studies in both neoplasms.

Case presentation: A 72-year-old patient with a history of CMML sought evaluation of growing bilateral testicular nodules. Solitary testicular lymphoma was suspected; orchidectomy was performed. The diagnosis of testicular RDD was established morphologically and confirmed immunohistochemically. Molecular analysis of testicular lesions and of archived patient bone marrow revealed the *KRAS* variant c 0.35 G>A / p.G12D in both, suggesting a clonal relationship.

Conclusion: These observations support classifying RDD as a neoplasm that can be clonally related to myeloid neoplasms.

1. Background

Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytosis (LCH) that most frequently presents as bilateral cervical lymphadenopathy in children and young adults. Extranodal manifestation, found in as many as 43 % of patients, primarily involves the skin (10 %), nasal cavity (11 %), bone (5–10 %) and central nervous system (5 %) [1]. The testes are seldom affected, with only 9 reported cases of testicular RDD (Table 1) [2,3]. These reports permit 2 observations: 1) Testicular RDD often arises in association with other hematological neoplasms, like lymphomas or leukemias, and 2) it affects older patients, with an average age of manifestation of 52.3 years for testicular RDD versus 20.6 years for RDD in general ($p < 0.0001$) [1]. We here report a 72-year-old patient with bilateral testicular RDD clonally related to CMML.

2. Case presentation

A Caucasian 64-year-old man was first admitted to hospital in 2014 due to reduced general condition and mild cachexia. Computerized tomography (CT) revealed right lower lobe pneumonia and moderate hepatosplenomegaly. A severe monocytosis was found (absolute count of 7.60×10^9/L, relative count of 55 %). After successful antimicrobial therapy, bone marrow was sampled and an integrative diagnosis of

Abbreviations: AFP, α-fetoprotein; aCGH, array-based comparative genomic hybridization; CT, computerized tomography; CMML, chronic myelomonocytic leukemia; ECD, Erdheim-Chester disease; FL, follicular lymphoma; H&E, hematoxylin / eosin; HCL, hairy cell leukemia; NGS, next-generation sequencing; OCT, octamer binding transcription factor; RDD, Rosai-Dorfman disease; VAF, variant allele frequency.

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Table 1
clinicopathological characteristics of published cases of testicular RDD.

Case No.	Age	Associated neoplasm	Size (cm)	Other sites / abnormalities	Author	Genetic data	Follow-up
1	41		1.5	-	Wang et al.	-	
2	47	-	5.1	-	Wang et al.	-	No recurrence at 4 years
3	72	-	4.3	Pleural and pericardial effusions, fever	Wang et al.	-	Effusions and fever resolved after orchiectomy
4	4	-	N/A	Lymph nodes and skin	Azoury and Reed	-	Persistent generalized lymphadenopathy
5	63	-	N/A	Lymph nodes, kidney, adrenal gland	De Guzman et al.	-	Died 9 years after initial diagnosis
6	67	B-cell lymphoma	N/A	Kidney	Lossos et al.	-	No disease progression or recurrent lymphoma
7	47	-	2.3	-	Fernandopulle et al.	-	Asymptomatic after 4 months
8	42	Chronic lymphocytic leukemia	6, 5	-	Del Gobbo et al.	-	
9	68	-	4.5	Widespread retroperitoneal fibrosis	Del Gobbo et al.	-	
10 (present case)	72	Chronic myelomonocytic leukemia (CMML)	3.4, 4	-	This study	*KRAS* (c 0.35 G>A)	Asymptomatic after 9 months, no recurrence of CMML

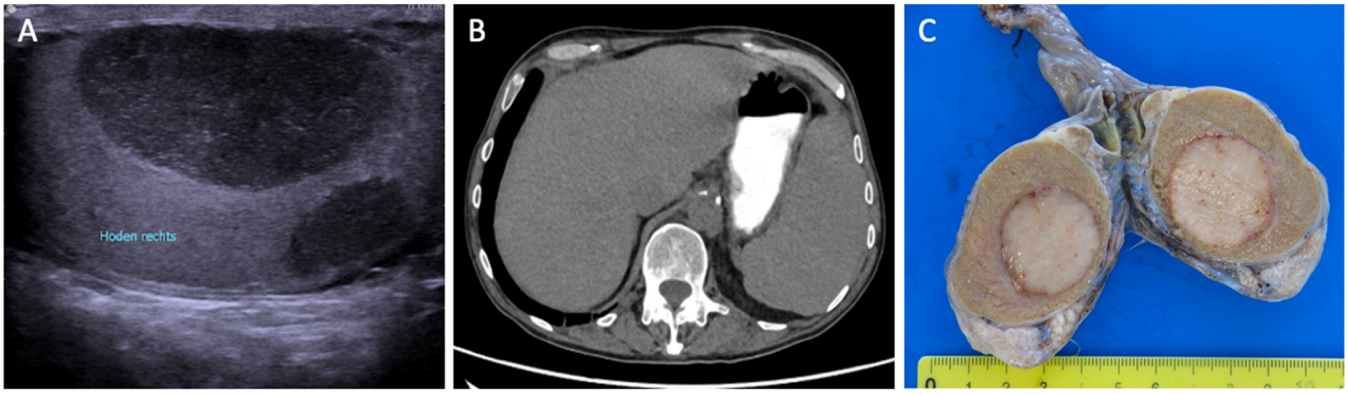

Fig. 1. A, Sonogram, right testicle, showing two well-defined hypoechogenic nodules. B, Axial CT image, upper abdomen, showing hepatosplenomegaly without parenchymal lesions. C, Photograph, bivalved right orchidectomy specimen, showing well-circumscribed yellowish-brown tumor-like nodules.

chronic myelomonocytic leukemia (CMML) was established. No systemic treatment was given as the CMML-Specific Prognostic Scoring System score was 0. The patient remained asymptomatic for 8 years before consulting a urologist with a complaint of increasing painless testicular nodularity and swelling over the preceding 3 weeks. He denied B symptoms, reported normal urinary continence and bladder control, and had no palpable lymphadenopathy. Sonography identified 3 hyperechogenic nodules with a maximum diameter of 3.4 cm in the left testis and 2 smaller nodules in the right testis (Fig. 1A). Testicular lymphoma was suspected. The patient was admitted to the Department of Urology. Staging CT found no lymphadenopathy, but hepatosplenomegaly was more pronounced than in 2014 (Fig. 1B).

Blood specimens revealed a mildly reduced estimated glomerular filtration rate of 85 ml/min. Serum values for several tumor biomarkers (serum ß-human chorionic gonadotropin, α-fetoprotein [AFP], lactate dehydrogenase) were within normal ranges, as were results of various other parameters, including coagulation studies. Five days after admission bilateral trans-scrotal orchidectomy was performed. The postoperative course was uneventful.

On macroscopic evaluation, the left orchidectomy specimen measured 6.5 × 4.8 × 4 cm and the right orchidectomy specimen measured 5 × 4×3.5 cm. Incision exposed 4 well-circumscribed glossy yellowish-brown nodules with a maximum diameter of 3.4 cm in the left testis and a similar nodule 4 cm in diameter in the right testis (Fig. 1C).

Histological evaluation revealed well-circumscribed tumorous lesions within the testicular parenchyma. These mainly consisted of large atypical histiocyte-like cells, lymphocytes and plasma cells. Residua of seminiferous tubules amid the lesion could be appreciated (Fig. 2A). The adjacent seminiferous tubules showed peripheral Sertoli cells and a reduced number of spermatocytes, without infiltration by neoplastic cells. Intratubular germ cell neoplasia was not detected and germ cell neoplasm or Leydig cell tumor were excluded as immunostaining identified no expression of inhibin, octamer binding transcription factor (OCT) 4, or AFP within the lesions. The proliferation rate, as assessed by immunostaining for the Ki-67 protein, was low (5 %). The atypical histiocyte-like cells displayed round to oval nuclei with prominent nucleoli and abundant pale to eosinophilic cytoplasm, features suspect for hematopoietic-system origin. They did not contain material that marked on periodic acid – Schiff staining; von Hansemann histiocytes with granular cytoplasm and Michaelis-Gutman bodies were not found, thus excluding malakoplakia. That they were of leukocytic origin was confirmed on immunostaining, as cytoplasm of virtually all lesional cells marked strongly for the leukocyte common antigen CD45. The large cells marked strongly for macrophage-associated antigens (CD68, CD163) and for histiocyte-associated antigens (CD14 and PU.1). Background inflammatory cells included plasma cells, CD4-expressing T-helper cells, CD20-expressing B lymphocytes, and polymorphonuclear neutrophil granulocytes. The histiocytic tumor cells exhibited emperipolesis (intracytoplasmic wholly entrapped intact lymphocytes and erythrocytes), the main diagnostic hallmark of RDD (Figs. 2B and 2C) and had an immunohistochemical profile typical of RDD, with S100 expressed (Fig. 2D) and CD1a absent (Fig. 2E). Immunostaining for OCT2, a highly sensitive marker for RDD [4,5], showed crisp nuclear marking in the neoplastic cells (Fig. 2F), confirming the diagnosis of

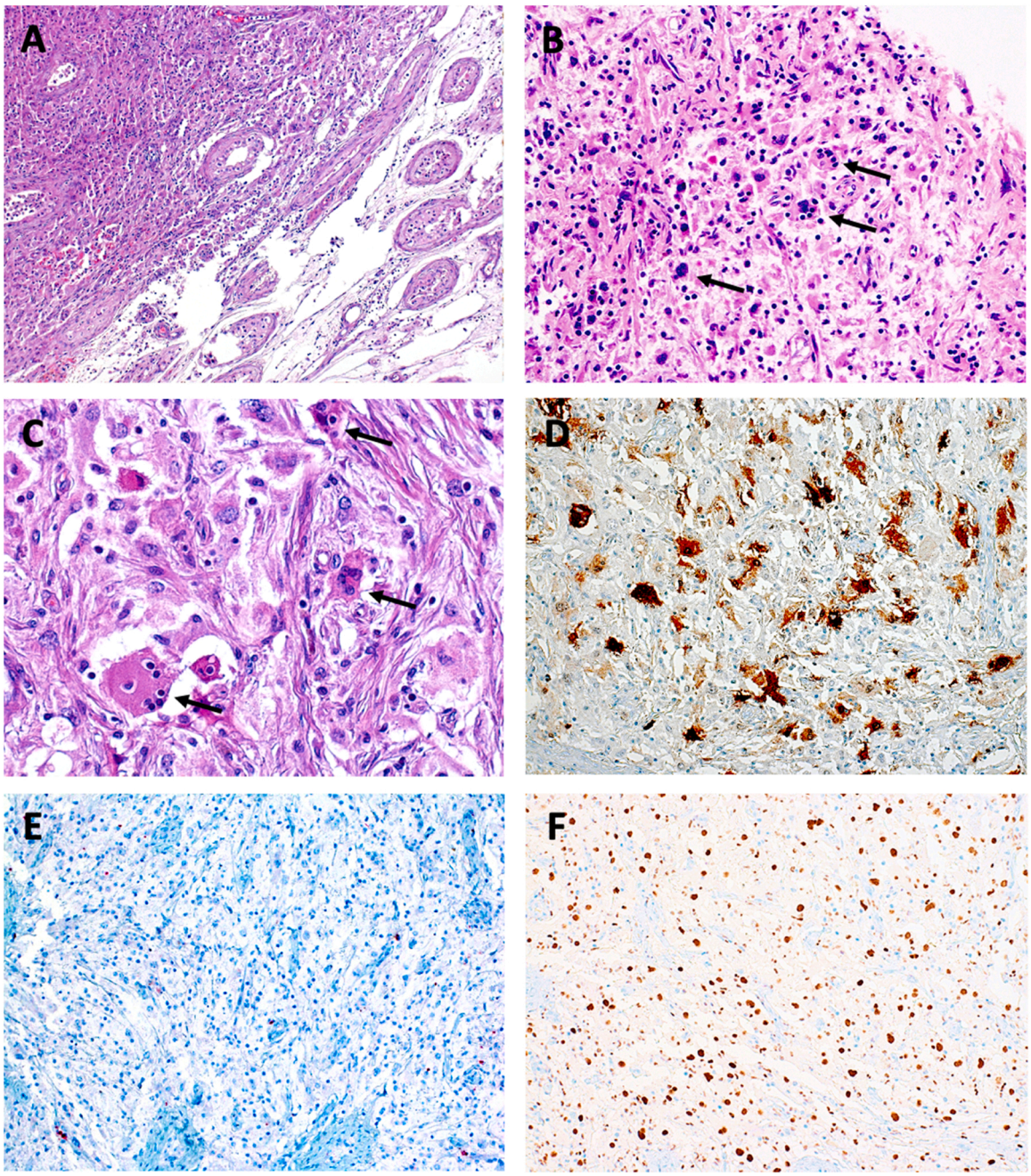

Fig. 2. A, On microscopy, the testicular tumors were composed of a lymphohistiocytic infiltrate adjacent to unremarkable seminiferous tubules (hematoxylin / eosin [H&E] x 40); B + C, atypical histiocytes with large nuclei, abundant eosinophilic cytoplasm, and prominent emperipolesis (arrow) (H&E 200 x and 400x, respectively); immunohistochemical staining, atypical histiocytes: D, S-100 (200x); E, CD1a (100x); F, OCT2 (100x).

testicular RDD.

To elucidate further the genetic alterations of RDD at this extremely rare anatomic site and to investigate a possible clonal relationship to the CMML, tumor DNA was extracted from formalin-fixed, paraffin-embedded testicular tumor samples and the 8-year-old archived bone marrow samples and tested by pyrosequencing (PyroMark Q24; Qiagen, Hilden, Germany) for hotspot mutations in *KRAS* (exons 2, 3, and 4), *NRAS* (exons 2, 3, and 4) and $BRAF^{V600E}$ (exon 15). A *KRAS* variant in exon 2 (NM_004985.5: c 0.35 G>A / p.G12D) was detected in RDD and CMML samples with variant allele frequencies (VAF) of 55 % and 61 % respectively.

To identify additional mutations and to compare both neoplasms genetically in more detail, next-generation sequencing (NGS) was performed using the Oncomine myeloid DNA panel covering 40 key DNA driver genes (Thermo Fisher Scientific, Waltham, MA). *KRAS* p.G12D was confirmed in both CMML and RDD samples, with VAF values of 70 % and 34 % respectively. No additional somatic mutations were detected in either testicular lesions or bone marrow.

Nine months after the initial diagnosis of RDD the patient is asymptomatic and has no signs of recurrence of RDD or progression of CMML.

3. Discussion and review of the literature

Recent advances in the understanding of various forms of histiocytosis, including RDD, are substantial: Firstly, mutations in the mitogen-activated protein kinase cell signaling pathway have been repeatedly detected, proving that RDD is a true neoplasm, rather than a reactive

process, as formerly postulated [1]. Secondly, histiocytoses often arise in association with clonally related hematologic neoplasms, such as leukemias or lymphomas [1,6–8]. Various studies have found the same oncogenic mutations in genes like *KRAS*, *BRAF*, *NRAS*, *ARAF*, and *MAP2K1* in paired neoplasms [1], as in our patient, suggesting clonal relationship and pointing towards a common cell of origin that gives rise to both neoplasms. Three models of transformation from primary hematologic malignancy to histiocytic neoplasm have been proposed: 1) direct transdifferentiation; 2) dedifferentiation and redifferentiation; 3) derivation of both neoplasms from a mutated progenitor in common [6]. Evidence favoring the third model includes presence of the variant $BRAF^{V600E}$ in histiocyte precursors like $CD11^{+}$ myeloid dendritic cells (DC), $CD14^{+}$ monocytes, and even bone-marrow $CD34^{+}$ hematopoietic stem/progenitor cells in histiocytoses like LCH or Erdheim-Chester disease (ECD) [9]. Both a histiocytic sarcoma and the follicular lymphoma (FL) alongside which it arose harbored clonal IGH rearrangements and t(14;18). Array-based comparative genomic hybridization (aCGH) identified gains and losses of genetic material only in the FL and not in the histiocytic sarcoma. [6] These findings argue against transdifferentiation or dedifferentiation and rather for a mutated progenitor cell in common, as these genetic aberrations, especially genomic losses, are irreversible.

Yet transdifferentiation may occur. Michonneau et al. described a patient with histiocytic sarcoma arising from clonally related hairy cell leukemia (HCL), both harboring the $BRAF^{V600E}$ variant. All cytogenetic alterations found in the patient's HCL using aCGH were also found in the histiocytic sarcoma. However, additional alterations were detected only in the histiocytic sarcoma, including a deletion of *E2A/TCF3*, a gene important in lymphoid lineage commitment, that might have promoted transdifferentiation from lymphoid to histiocytic lineage. A mutated progenitor in common could not be postulated in this patient, as $BRAF^{V600E}$ was not detected in CD14 blood monocytes [7].

In analogy with RDD, blastic plasmacytoid dendritic cell neoplasm (BPDCN) can be associated with myeloproliferative/myelodysplastic neoplasms in up to 20 % of patients [10]; recent reports have found common clonal genetic alterations in CMML and BPDCN, including 12p13/ETV6 deletions, complex karyotypes, copy number losses in tumor suppressor genes (e.g., CDKN2A, CDKN1B, RB1, and NR3C1) and mutations in genes involved in epigenetic regulation (e.g. TET2, ASXL1). [11–13] Morphologically, BPDCN exhibits intermediate sized tumor cells resembling lymphoblasts or myeloblasts with scanty cytoplasm and eccentric nuclei with characteristic expression of CD123 and TCF4. [14] The absence of emperipolesis and histiocyte- and RDD-specific antigens such as CD14, PU.1 and Oct2 can further facilitate the distinction from RDD.

The association of clonal hematopoiesis of indeterminate potential (CHIP) and myeloid neoplasms is well established [15]. Interestingly, NGS analyses of bone marrow in ECD patients found a high frequency of CHIP- and myeloid-malignancy – associated mutations in genes like *TET2*, *ASXL1*, and *DNMT3A* [16]. As these mutations might represent early events in the development of ECD and associated myeloid neoplasms, further studies should address their role in other histiocytoses, like RDD.

Targeted therapies have shown good efficacy in 2 patients with refractory RDD. Mastropolo et al. described a 7-year-old child with an overlap of LCH and RDD in a cerebral lesion [17]. After the $BRAF^{V600E}$ variant was detected in peripheral blood mononuclear cells using quantitative polymerase chain reaction, the patient responded well to the *BRAF* inhibitors dabrafenib and trametinib [17]. In another patient described by Jacobsen et al. RDD with an activating *KRAS* mutation was efficiently treated in an experimental protocol deploying cobimetinib [18]. These encouraging reports underscore the necessity to find novel mutations amenable to targeted therapies.

In conclusion, to have detected the oncogenic *KRAS* variant c 0.35 G>A in our patient's RDD and CMML provides further evidence for a clonal relationship between histiocytoses and myeloid neoplasms. Whilst occurrence *de* novo of the same variant in both neoplasms independently cannot completely be excluded, it seems very unlikely. In contrast to other forms of histiocytoses, only a few studies have provided molecular data regarding both RDD and associated hematologic neoplasms [19,20]. Our report is the first providing detailed molecular analyses of testicular RDD and the third report of testicular RDD in documented association with hematologic neoplasia. The histological and molecular findings and consideration of differential diagnoses that we present may contribute to more precise diagnostic evaluation and pathophysiologic understanding of RDD at this uncommon site.

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Credit authorship contribution statement

Conceptualization, **A.F.** and **S.D.**; data curation, **A.F.**, **D.J.**, **J.B.**, **S. De.**, **A.B.**, **F.O.**, **S.M.**, and **F.B.**; formal analysis, **F.O.**, **S.D.**, and **A.F.**; resources, **A.F.**, **J.B.**, **F.O.**, **S.M.**, and **F.B.**; supervision, **F.O.**, **S.De.**, and **S.D.**; project administration, **F.O.** and **A.F.**; Writing—original draft, **A. F.**; and writing—review & editing, **S.D.**, **D.J.**, **A.B.**, and **F.O.** All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This case report has been assembled in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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