ROSE in Rosai–Dorfman–Destombes (RDD) disease: a cytological diagnosis

Santosh Tummidi1*, Hemant Kumar Singh2, Prudhvinath A Reddy3, Manda Sindhura1, Navya Kosaraju3, Arundhati Shankaralingappa1 and Naresh P Kumar2

Abstract
Background: Rosai–Dorfman–Destombes (RDD) is also known as sinus histiocytosis with massive lymphadenopathy (SHML). It is a benign proliferative disorder of histiocytes, affecting lymph nodes, rarely with extra-nodal involvement. Rapid on-site evaluation (ROSE) with fine-needle aspiration cytology (FNAC) can be utilized as a minimally invasive investigation to avoid unnecessary surgery of this self-limiting disease.

Case presentation: A 65-year-old female presented with complaints of bilateral cervical lymphadenopathy since 1 year. Rapid on-site stain with FNAC from bilateral cervical lymph nodes revealed features of Rosai–Dorfman–Destombes (RDD) disease.

Conclusion: FNAC with rapid on-site evaluation can provide a simple and cost-effective method for looking at the unique cytological features of the disease and act as a first-line investigation.

Keywords: Rapid on-site evaluation, Cytology, Cellblock, Rosai–Dorfman–Destombes, Emperipolesis, Plasma cell

Background
Rosai–Dorfman–Destombes (RDD) disease, also called SHML (sinus histiocytosis with massive lymphadenopathy), is an idiopathic lymph node-based histiocytic proliferative disorder. 20–50% of patients with nodal/cutaneous disease undergo spontaneous remission [1, 2]. The clinical findings in such cases can include painless enlargement of the cervical lymph nodes, fever, leukocytosis, anemia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate (ESR) [3]. Rapid on-site evaluation (ROSE) with fine-needle aspiration cytology (FNAC) is a cost-effective, rapid method that can be used for cytological diagnosis of RDD [4]. Cytology can virtually obviate the need for biopsy in most cases, due to its classic morphological resemblance to histopathological features.

Case presentation
A 65-year-old female presented to our general surgery outpatient department with complaints of bilateral neck swelling of 1 year duration. Her past medical history included cervical carcinoma diagnosed and treated in 1991, hypertension, and coronary artery disease treated with stenting via the external iliac and femoral artery route in 2016. She had no history of night sweats, loss of appetite, weight loss, or evening rise of temperature. She had no other swellings in the body. On examination, she had multiple, bilateral enlarged cervical lymph nodes, including level IB, V on the left side, and level IIB, III on the right. The multiple matted lymph nodes were soft and non-tender on palpitation, with the largest node measuring 2 × 2 cm in the left IB cluster (Fig. 1a–c). She had no significant axillary or inguinal lymph node enlargement. The per-abdominal examination did not reveal hepatosplenomegaly and the oro-pharyngeal-laryngeal examination was unremarkable.

Her serum thyroid profile showed a T3 of 1.02 ng/ml (normal: 0.80–2.0), T4 of 9.9 µg/dl (normal: 5.1 to 14.1),...
and TSH 3.65 µU/ml (normal: 0.27 to 4.20). Random blood sugar was within normal limits (91 mg/dl). Her albumin was 3.7 g/dl (normal: 3.9 to 5.0) and globulin was 5.6 g/dl (normal: 2.0 to 3.5). She had an elevated total protein of 9.3 g/dl (normal: 6.5–7.8 g/dl). Her blood hemogram showed a hemoglobin of 8.9 g/dl (normal: 12–15 g/dl), a total leucocyte count of 4660 cells/mm³ (normal: 4000–10,000 cells/mm³), differential leucocyte count of N56, L34, M07, E03, and B00, and a platelet count of 305,000/mm³ (normal: 150,000–410,000/mm³). Her peripheral blood picture revealed features of microcytic hypochromic anemia. The erythrocyte sedimentation rate was 100 mm/h (normal: 0–30 mm/h). Her serological markers for hepatitis B, hepatitis C, and human immunodeficiency virus were negative using the lateral-flow card method.

Her chest radiograph showed prominent, bilateral hilar shadows with clear, bilateral lung fields (Fig. 1d). The ultrasound (USG) neck revealed multiple, bilateral enlarged cervical lymph nodes involving levels IB, II, III and IV. The largest lymph node measured 2.4 × 1.0 cm in size and was located in the level 1B group, on the left side. Some of the enlarged lymph nodes were round in shape and hypoechoic (Fig. 1e). USG thyroid showed iso- to hyper-echoic solid nodules measuring 1.1 × 0.6 cm in size, in the left lobe, with peripheral calcification. The right lobe also showed a small sub-centimetric nodule with peripheral calcification. The isthmus was normal. A provisional differential diagnosis of tubercular lymphadenopathy; carcinoma thyroid with possible lymph node metastasis; and lymphoma were considered. FNAC from thyroid and cervical lymph nodes was advised.
Rapid on-site evaluation (ROSE) using 1% aq. toluidine blue solution was employed for the aspirate retrieved from the thyroid swelling (under ultrasound guidance). The specimen showed mild cellularity comprising thyroid follicular cells in monolayered sheets with scattered single cells. The thyroid follicular cells showed mild-to-moderate nuclear pleomorphism with scant cytoplasm. A few Hurthle cells and pigment-laden cyst macrophages were also seen (Fig. 2a). The background showed a thin colloidal material with focal calcification and areas of hemorrhage (Fig. 2b).

ROSE-stained slides from the left cervical level IB and right level IIB groups showed cellular features comprising mature small and large lymphocytes in various stages of maturation. Numerous emperipolesis bodies were also noted with engulfed lymphocytes, plasma cells, red blood cells (RBC), neutrophils and degenerate cells with abundant eosinophilic cytoplasm and multiple, eccentrically placed nuclei (Fig. 2c, d). The slides were then returned for routine cytology staining with Giemsa and Papanicolaou stains. Cytosmears also revealed similar features of emperipolesis bodies with lymphocytes, plasma cells and multinucleated histiocytes. The background showed lympho-glandular bodies with few multinucleated giant cells (Fig. 3a–d). There was no evidence of granuloma or necrosis in the cytosmears. Ziehl–Neelsen stain for acid-fast bacilli was negative. FNAC showed features of Rosai–Dorfman–Destombes (RDD) disease with the thyroid showing colloid goiter with cystic degeneration. Hence, the patient was diagnosed with classical nodal RDD.

Cellblock preparation from the lymph node aspirate showed lymphoid follicles with germinal centers replete with foamy histiocytes containing engulfed plasma cells, lymphocytes and neutrophils. Few scattered plasma cells were also seen in the background (Fig. 4a–d). Immunohistochemistry for S100 was positive and CD1a was negative (Fig. 4e).

**Fig. 2**

a Cytosmears are showing mild cellularity comprising thyroid follicular cells in monolayered sheets with mild nuclear pleomorphism and scant cytoplasm. Few with pigment laden are also seen. b Focal calcification and areas of hemorrhage are also seen [Tol blue, x 40]. c, d Cytosmears were cellular comprising numerous histiocytes with emperipolesis body having engulfed lymphocytes, plasma cells, RBCs, neutrophils, degenerated cells with abundant eosinophilic cytoplasm and eccentrically placed multiple nuclei. [Tol blue, x 10 and x 40]
The patient was started on prednisolone 1 mg/kg/day. After 8 weeks, she showed partial response and the patient is currently on low-dose steroids and follow-up.

Discussion

RDD is a well-defined clinicopathological entity, first described by Destombes in 1965 [1, 5]. Later in 1969, Juan Rosai and Ronald Dorfman, recognized it as a distinct disease entity comprising sinus histiocytosis and massive lymphadenopathy [5, 6]. 20–50% of RDD patients with nodal/cutaneous disease undergo spontaneous remission [2]. Possible infection and immunodeficiency have been suggested as causes of RDD. Association with HHV6, EBV, Klebsiella spp., and CMV has been cited, but no definite etiological link with RDD has been confirmed [6–8]. RDD is also associated with the H syndrome (SLC29A3 gene), Hodgkin disease, acute leukemia, sarcoma, and immunologic/IgG4 syndrome [2, 9].

RDD is considered to be a self-limiting disorder of an unknown etiology. Clonality studies suggest that lesional RDD cells are polyclonal, reactive, and non-neoplastic. Recent studies identified NRAS, KRAS, MAP2K1, and ARAF mutations in patients with features of RDD [2].

Although any age group can be involved, 80% of the cases manifest in the first two decades of life with a male predilection (male:female = 2:1). RDD presents with gradual onset, painless, massive cervical lymphadenopathy, with fever, leukocytosis, elevated ESR, hypogammaglobulinemia, and occasional anemia [1, 10, 11]. Similar findings were noted in our patient. Other lymph nodes, i.e., mediastinal, axillary, inguinal, and para-aortic lymph nodes have also been found affected in RDD. In 40–45% of patients, extra-nodal sites like skin, central nervous system, lungs, cardiothoracic region, subcutaneous tissue, salivary glands, orbits, bone marrow, breasts, thyroid, cervix, and kidneys have also been found affected [12, 13].

Rapid on-site evaluation with fine-needle aspiration cytology can be a useful, cost-effective technique for the diagnosis of RDD [2]. To our knowledge, our case report is the first in the literature to describe ROSE findings of RDD along with the utility of cell blocks for improving the efficacy of FNAC. Aspiration from the
Lesion showed proliferation of histiocytes with abundant eosinophilic to vacuolated cytoplasm, vesicular single to multiple nuclei, and lymphophagocytosis or emperipolesis in a reactive inflammatory background (lymphocytes in early-stage and plasma cells in later stages). The lymphocytes inside the histocyte have a halo around them, which is not seen in the tissue section due to fixation artifacts [6, 11]. Less often, neutrophils and RBCs can also be seen. FNA may be sufficient to make the diagnosis in most cases thus preventing unnecessary invasive procedures [1, 3, 14, 15].

Histologically, there is an infiltration of the tissue by lymphocytes, histiocytes, and plasma cells. The presence of emperipolesis (histiocytes with engulfed lymphocytes, erythrocytes, and plasma cells) is usually characteristic of Rosai–Dorfman–Destombes disease along with dilated sinusoids [6]. The diagnosis can be confirmed by using immunohistochemical (IHC) markers. Characteristically, S100 is always positive along with other markers, like CD68, CD163, α1 anti-chymotrypsin, and α1 anti-trypsin, with negative results for CD1a and Lagerin (CD207) [11, 12].

The differential diagnoses can include reactive lymph node hyperplasia, infectious lymphadenitis, Langerhans cell histiocytosis, non-Hodgkin’s lymphoma, and metastatic carcinoma [3, 12] (Table 1).

RDD has no specific treatment since some patients undergo spontaneous resolution [10]. Surgery may be performed in cases with obstructive/compressive symptoms to vital organs, airway, or with cosmetic issues [5]. Other modalities such as chemotherapy, corticosteroids, low-dose interferon, antibiotics, and radiotherapy have been attempted with variable results. However, the best treatment for RDD is yet to be established [1].

**Conclusion**

The cytological features of RDD are so distinctive that they can be diagnosed by FNAC. Implementation of ROSE provides added benefit for collecting samples for cell blocks and IHC, hence obviating the need for invasive investigations. Clinicians and cytopathologists should...
have a high degree of suspicion for RDD in patients with massive bilateral lymphadenopathy.

Abbreviations

CD: Cluster of differentiation; CMV: Cytomegalovirus; EBV: Epstein–Barr virus; FNAC: Fine needle aspiration cytology; HHV: Human herpes virus; RDD: Rosai–Dorfman–Destombes; ROSE: Rapid on-site evaluation; USG: Ultrasonography.

Acknowledgements

We express deep sense of gratitude to Mr. Shesh KB, Mr. Nagarjuna K, Mr. Raju VVSN and Mr. Ramana BB for their technical support with USG guided cytology and cell block preparation.

Authors’ contributions

TS carried out concepts and design, literature search, manuscript preparation, participated in the clinical study and will stand as guarantor. HKS carried out data acquisition, data analysis. PRA, MS, NK carried out concepts and design, literature search. AS, NKP carried out concepts and design, data analysis and literature search. All authors read and approved the final manuscript.

Funding

Not available.

Availability of data and materials

All the data regarding the findings are available within the manuscript.

Declarations

Ethics approval and consent to participate

This case report was conducted in accordance with the fundamental principles of the Declaration of Helsinki.

Consent for publication

Written consent for the publication and any additional related information was taken from the patient involved in the study.

Competing interests

The authors declare that they have no competing interests.

Author details

1 Department of Pathology, AIIMS, Mangalagiri, Guntur, A.P., India 522503. 2 Department of General Surgery, AIIMS, Mangalagiri, Guntur, A.P., India 522503. 3 Department of Radiodiagnosis, AIIMS, Mangalagiri, Guntur, A.P., India 522503.

Received: 12 February 2021 Accepted: 2 April 2021

Published online: 13 April 2021

References

1. Rajyalakshmi R, Akhtar M, Swathi Y, Chakravarthi R, Bhaskara Reddy J, Beulah PM. Cytological diagnosis of Rosai-Dorfman Disease: a study of twelve cases with emphasis on diagnostic challenges. J Cytol. 2020;37(1):46–52.
2. Abla O, Jacobsen E, Picarsic J, et al. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood. 2018;131(26):2877–90.
3. Hussain A, Tandon A, Prayaga AK, Paul TR, Narendra AM. Cytomorphology and histology correlation of Rosai-Dorfman disease: a 15-Year Study from a Tertiary Referral Centre in South India. Acta Cytol. 2017;61(1):55–61.
4. Kanchan K, Santosh T, Agnihotri M, Sathe P, Naik L. This ‘Rose’ has no thorns - diagnostic utility of ‘Rapid On-Site Evaluation’ (Rose) In Fine Needle Aspiration Cytology. Indian J Surg Oncol. 2019;10(4):688–98.
5. Aziz M, Ray PS, Haider N, Rathore SP. Diagnosis of Rosai-Dorfman disease in elderly female on fine needle aspiration cytology: a case report. Case Rep Pathol. 2012. https://doi.org/10.1155/2012/806130.
6. Sall A, Toure AO, Ndiaye FS, Sene A, Sall FB, Faye BF, Seck M, Diop S. Rosai Dorfman disease diagnosed by fine-needle aspiration cytology in a young man with HIV infection. Clin Case Rep. 2015;3(10):879–83.
7. Kushwaha R, Aahuwalia C, Sipayva V. Diagnosis of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) by fine needle aspiration cytology. J Cytol. 2009;26(2):83–5.

Table 1

| Disease                     | Clinical features                          | Cytology                                                                 | IHC                        |
|-----------------------------|--------------------------------------------|--------------------------------------------------------------------------|----------------------------|
| Rosai Dorfman disease       | Children's and young adults, M > F, painless lymphadenopathy, extranodal presentation seen | Histioctyes with vesicular nucleus and abundant clear cytoplasm, with fine vacuoles and lymphocytes, reactive background of lymphocytes, plasma cells, neutrophils | S100, CD68 positive, CD1a negative |
| Reactive lymph node hyperplasia | Malaise, painless lymphadenopathy, self-limited disease | Neutrophils, histocytes may or may not be present,                        | Histiocytes negative for S100 |
| LCH                         | Localized or multiple lesions with disseminated disease. Nodal involvement may be sole manifestation, bone lesion may be seen | Polymorphic infiltrate with eosinophils and histiocytes with cleaved nucleus | CD1a positive               |
| Hemophagocytic lymphohistiocytosis | May be associated with malignancy of hematological origin, multi organ failure, pancytopenia, Hepatosplenomegaly | Benign histiocytes with engulfed platelets and RBCs                     | CD68 positive               |
| Non-Hodgkin's lymphoma      | Lymphadenopathy, B symptoms weight loss, fever, loss of appetite | Mononuclear population of lymphoid cells                                 | Depends of cell of origin   |
| Hodgkin lymphoma            | Lymphadenopathy with B symptoms            | Polymorphic population with small lymphocytes, eosinophils, plasma cells, and RS cells | RS cell positive for CD15 and CD30 |
| Metastatic carcinomas       | Primary in any organ                      | Lymphoid population with metastatic tumor cells resemblance to primary organ morphology | Depends on organ of origin  |
8. Sheela KM, Elizabeth R, Divya R. Cytological and histopathological diagnosis of a multifocal Rosai Dorfman disease with involvement of pinna: a rare case report. Trop J Path Micro. 2018;4(8):551–5.
9. Emile JF, Abila O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016;127(22):2672–81.
10. Ekhart VR, Shelkar RN, Rane S, Anand A, Lanjewar K, Jain SKT. Rosai-Dorfman Disease: a rare cause of cervical lymphadenopathy. Int J Head and Neck Surg. 2014;5(3):152–4.
11. Abraham LK, Pulickal SG, Poothiode U. A case of cutaneous Rosai-Dorfman disease diagnosed by fine needle aspiration cytology. Int J Res Dermatol. 2015;1:20–3.
12. Garza-Guajardo R, Garcia-Labastida LE, Rodriguez-Sanchez IP, Gomez-Macias GS, Delgado-Enciso I, Chaparro MM, Barboza-Quintana O. Cytological diagnosis of Rosai-Dorfman disease: a case report and revision of the literature. Biomed Rep. 2017;6(1):27–31.
13. Deshpande V, Verma K. Fine needle aspiration (FNA) cytology of Rosai Dorfman disease. Cytopathology. 1998;9(5):329–35.
14. Kumar B, Karki S, Paudyal P. Diagnosis of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) by fine needle aspiration cytology. Diagn Cytopathol. 2008;36(10):691–5.
15. Jena M. Diagnosis of Rosai-Dorfman disease by fine needle aspiration cytology in a case with cervical lymphadenopathy and nasal mass. Online J of Health and Allied Sci. 2011;10(2):1–3.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.
Learn more biomedcentral.com/submissions