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Review Article

Rosai-Dorfman disease and Hodgkin lymphoma synchronously involving the same lymph node: A rare case report with review of literature

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ABSTRACT

Rosai-Dorfman disease (RDD) is usually a self-limiting pseudolymphomatous condition of unknown cause. Most common presentation is painless cervical lymph nodes. The association of RDD with lymphoma has been rarely described in literature, most of them being non-Hodgkin lymphoma (NHL). Its association with Hodgkin lymphoma (HL) is very rarely reported. We report a patient with HL and RDD involving the same lymph node concurrently. Both the areas were confirmed by histomorphology and immunohistochemistry (IHC). The detection of RDD in lymphoma cases is incidental and seems to have no clinical significance. Thus, finding of focal RDD does not affect therapeutic decisions of these patients. However, admixture of lymphoma cell population (both HL and NHL) along with histiocytic proliferation can be a diagnostic challenge at times, especially in inexperienced hands and a resource-limited setup where IHC is not available.

1. Introduction

Rosai-Dorfman disease (RDD) was first described as a distinct entity by Rosai and Dorfman in 1969. It is usually a self-limiting pseudolymphomatous condition of unknown cause. Most common presentation is painless cervical lymph nodes. Fever, leukocytosis, anemia, elevated erythrocyte sedimentation rate (ESR), and polyclonal hypergammaglobulinemia are the clinical parameters usually associated with it. Lymphadenopathy occurs as a result of the expansion of sinuses, with benign histiocytes usually showing emperipolesis of lymphocytes along with infiltrates of plasma cells into the medullary cords. Mass lesions in the extranodal sites have been reported in approximately 30% of patients.[1]

Although RDD has a benign clinical course, fatality is reported in up to 10% of cases, particularly in patients who have immunologic abnormalities.[2]

The association of RDD with lymphoma has been rarely described in literature, most of them being non-Hodgkin lymphoma (NHL). Its association with Hodgkin lymphoma (HL) is very rarely reported.

We herein report a patient with HL and RDD involving the same lymph node concurrently.

2. Case report

A 41-year-old female patient presented with swelling in the left submandibular region. Blood investigations revealed raised ESR and normal complete blood count. Liver function test was largely normal with mild decrease in total protein. Thyroid profile was normal.

Fine-needle aspiration from the left submandibular swelling was performed, which reported reactive lymphadenitis.

A biopsy was subsequently performed in the same site in May 2017. We received two lymph nodes measuring $4 \times 2 \times 1.5$ cm and $1.5 \times 1 \times 0.8$ cm. Cut surfaces of the lymph nodes were grayish white and lobulated.

3. Results

Histologic sections of the lymph nodes revealed effacement of nodal architecture by a tumor (Fig. 1A). The tumor had a nodular and focal diffuse architecture. Large atypical lymphoid cells were

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seen scattered singly, in loose groups, and as small sheets. Cells had high N/C ratio, vesicular nuclei, prominent nucleoli, and moderate amount of pale eosinophilic cytoplasm. Tumor cells were predominantly mononuclear with many admixed multilobated and occasional binucleated forms (Fig. 1B). Background cells were predominantly mature small lymphocytes and histiocytes. There was paucity of granulocytes including eosinophils and neutrophils in the background population of cells. On IHC, the large atypical lymphoid cells were heterogeneously positive for CD20 (Fig. 1C) and leukocyte common antigen (LCA) and diffusely positive for BCL6. These cells were negative for CD30, CD3, epithelial membrane antigen (EMA), fascin, and Epstein-Bar virus (EBV). Collarettes of T lymphocytes around the large atypical cells were highlighted by CD3 staining (Fig. 1D). Scattered immunoblasts were positive for CD30.

Also seen were multiple large foci of pale histiocytic cells arranged in loose sheets and clusters and scattered singly, against a background of mature lymphocytes and plasma cells (Fig. 2A). These histiocytic cells were large with abundant pale cytoplasm, small ovoid vesicular nuclei, and conspicuous nucleoli. Many of these histiocytes showed evidence of emperipolesis (Fig. 2A, inset). These foci were admixed with previously described tumor areas (Fig. 1A). IHC highlighted different staining patterns in these areas. The pale histiocytic areas were strongly positive for s-100 (Fig. 2B), weakly positive for CD68, and negative for CD1a.

Thus, the final diagnosis of nodular lymphocyte predominant–type HL (NLPHL) with coexistent RDD was made. The patient is on regular follow-up with the oncologist since 2 years and has not been given any treatment after excision.

4. Discussion

Etiology of RDD is still unknown. It can occur sporadically, with occasional clustering, which suggests a genetic or an infectious component. EBV and human herpes virus 6 (HHV-6) are proposed to be the infectious agents. Recently, other disease-causing agents such as Varicella zoster virus, cytomegalovirus, *Brucella* spp, and *Klebsiella* spp have been implicated.[3,4]

Association between RDD and lymphoma is rare. On reviewing the literature, we identified fifteen reported cases. Five of these fifteen patients had RDD and NHL, both presenting in different anatomic sites with a time interval ranging from 8 months to 12 years. Two of these fifteen cases presented with NHL and RDD concurrently but at different anatomic sites.[2,8–13] Previously, eight cases have also been reported with RDD and lymphoma involving the same lymph node concurrently. Two of these eight cases were of NHL, and the others were reported as HL (Table 1).

In our study, we describe a case of NLPHL and RDD involving the same lymph node concurrently. This case showed multiple small foci of RDD having characteristic histomorphology and IHC features.

It is known that the RDD cells share some IHC markers with the cells of Langerhans cell histiocytosis, such as S-100. However, RDD cells generally do not express CD1a, which is normally expressed by Langerhans cells. In our case also, the histiocytes were positive for S-100 and negative for CD1a, thus proving their nature.

The cause and pathogenesis of RDD associated with lymphoma cases remains largely unknown, as is the pathogenesis of RDD. Various studies however have given explanation for this association, the common denominator for both these disease processes being abnormalities related to the immune system.[2]

HHV-6 mostly infects individuals in childhood causing latent infections for years in host cells. This infection can be reactivated by immunodeficiency. It has been suggested that the foci of RDD are related to immunodeficiency associated with the presence of lymphoma, which predisposes to reactivation of HHV-6 infection. However, whether HHV-6 directly causes RDD or is an innocent bystander is not known.[5]

While reviewing the reported cases, we found that most cases of concurrent involvement were with HL, the predominant type being NLPHL which is the histological subtype having least association

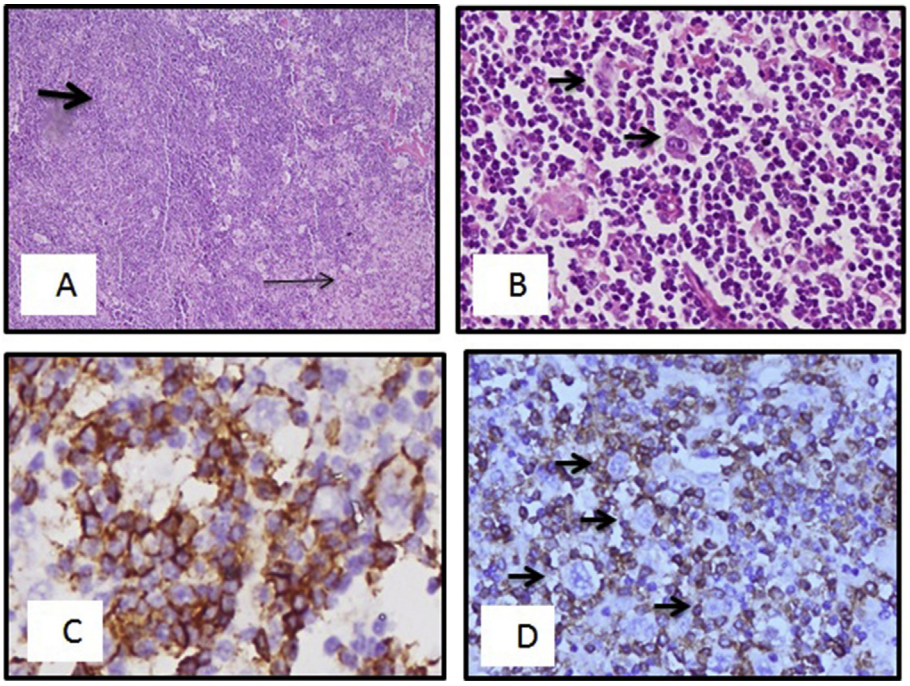

Fig. 1. (A) Effacement of nodal architecture by a tumor (thick arrow) interspersed with paler histiocytic areas (thin arrow). (B) Tumor area comprising singly scattered atypical lymphoid cells, most of them being mononuclear cells having prominent nucleoli (arrows). (C) These large cells were positive for CD20. (D) CD3-positive T-cell collarette around tumor cells (arrows).

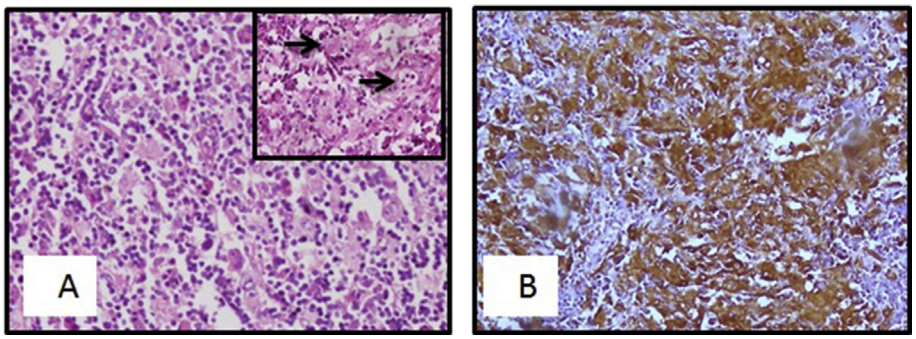

Fig. 2. (A) In pale histiocytic areas, cells were arranged in loose sheets and clusters, with histiocytes showing emperipolesis (inset, arrows). (B) These cells were strongly positive for s100.

Table 1
Coexistent lymphoma and RDD involving the same lymph node.

S No.	References	Age/Sex	Type of lymphoma	Size of RDD	LN site
1	Falk et al.,[6] 1991	49/M	Hodgkin disease, mixed cellularity	–	Retroperitoneal
2		24/M	Hodgkin disease, NOS		Cervical
3	Maia et al.,[14] 1995	39/M	Hodgkin disease, NLPHL	–	Cervical
4		11/M	Hodgkin's disease, NLPHL		Mediastinal
5	Lu et al.,[7] 2000	62/F	Follicular lymphoma, grade 2	8 mm	Inguinal
6		30/F	Hodgkin disease, NLPHL	2 mm	Axillary
7		28/M	Hodgkin disease, NLPHL	2 mm & 3 mm	Cervical
8		63/F	Follicular lymphoma, grade 1	6 mm	Inguinal
9	Present case	41/F	Hodgkin lymphoma, NLPHL	1.2 cm	Submandibular (cervical)

RDD, Rosai-Dorfman disease; LN, lymph node; NLPHL, nodular lymphocyte predominant–type HL; NOS, not otherwise specified.

with EBV (5%). Therefore, EBV is probably not the causative agent of RDD. However, RDD could still represent an aberrant histiocytic response to EBV infection.

Alternatively, it is also conceivable that the secretion of certain cytokines, e.g., interleukins, by the neoplastic cells of HL may cause the development of RDD-like changes in affected lymph nodes by inducing the differentiation of monocytes into functionally activated macrophages with the same immunophenotype as RDD cells.[6]

Lu et al.[7] reported a series of four cases with concurrent occurrence of RDD and lymphoma. All the cases had a small RDD focus varying between 2 mm and 8 mm in size, with histomorphology and IHC confirming the diagnosis. Our patient did not have evidence of RDD in any other nodal or extranodal sites. It was seen as multiple focal aggregates (largest measuring 1.2 cm in size) occupying less than 10% of the lymph node tissue sampled and interspersed with lymphoma cell population. Our case represents the largest focus of RDD reported in association with NLPHL.

The detection of RDD in lymphoma cases is incidental and seems to have no clinical significance. Thus, finding of focal RDD does not affect therapeutic decisions of these patients. However, admixture of lymphoma cell population (both HL and NHL) along with histiocytic proliferation can be a diagnostic challenge at times, especially in inexperienced hands and in a resource-limited setup where IHC is not available. These histomorphological features can be mimicked by various conditions such as Langerhans cell histiocytosis, xanthogranulomatous lesions, hemophagocytic syndromes, and reactive histiocytic proliferations. The problem is aggravated in small/trucut biopsies in which a large focus of RDD can mask the underlying lymphoma because of sampling error, leading to misdiagnosis.

5. Conclusion

The coexistence of lymphoma and RDD in the same lymph node suggests a possible link in the pathogenesis of these diseases. This link seems particularly likely for NLPHL, considering the relative rarity of this neoplasm as such but its common occurrence with RDD. Although this association carries no prognostic or therapeutic implication, pathologists should be aware of this phenomenon, especially when dealing with trucut biopsies of lymph nodes showing features of RDD as there can be underlying lymphoma masked by these areas leading to erroneous interpretation. Careful search, IHC findings, and clinical correlation can help in arriving at correct diagnosis.

Conflict of interest

Both the authors have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmrp.2019.09.001.

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