Rosai Dorfman disease diagnosed by fine-needle aspiration cytology in a young man with HIV infection

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Key Clinical Message
RDD (Rosai Dorfman disease) is a rare and benign histiocytic proliferative disorder of unknown etiology. FNAC (Fine-needle aspiration cytology) is a useful and reliable tool for the diagnosis of RDD, and as such, biopsy is avoidable.

Keywords
Emperipolesis, Fine-needle aspiration cytology, HIV, Rosai Dorfman disease.

Introduction
RDD (Rosai Dorfman disease), also called SHML (sinus histiocytosis with massive lymphadenopathy), was first described by Rosai and Dorfman in 1969 [1]. RDD is a rare and self-limiting disorder that more frequently affects children, adolescents, and young men; however, it can occur in adults and the elderly [2]. Its main clinical manifestation is painless cervical lymph node involvement, but other lymph nodes can also be involved. Involvement in extranodal sites, such as the skin, brain, pericardium, scrotum, bone, eyes, upper respiratory tract, breast, heart, thyroid, etc. have also been described [2-8]. In a recent study, purely extranodal RDD cases were reported to occur more commonly than purely nodal cases (77% vs. 8%) [9]. The exact etiology and pathogenesis of RDD are not fully understood. Some viruses, such as EBV (Epstein-Barr virus) and human herpes virus 6 (HHV6), have been, suggested to be the causative agents of RDD, but concrete evidence is still lacking [10, 11]. Few RDD cases that were associated with HIV infection have been described in the literature. Here, we report cytologic findings after FNA (fine needle aspiration) in a patient with RDD and HIV infection.

Case report
A man infected with type 1 HIV sought consultation for cervical swelling that had rapidly evolved over 4 months. He also complained of night sweats, but had no history of fever or weight loss.

Physical examination revealed swollen cervical lymph nodes with diameters of up to 3 cm that were firm, painless, and bilateral, but not symmetrical. The other ganglionic areas were free of swollen lymph nodes. The blood count results were as follows: hemoglobin = 10.2 g/dL, MCV = 84 FL, WBC = 7.8 G/L, platelet count = 189 G/L, neutrophil count = 3.8 G/L, and lymphocyte count = 2.1 G/L. No abnormal cells were observed on the blood smear.

A cervical lymph node sample obtained by FNA and stained with MGG revealed the following findings (fig. 1):

- Low power examination (×10, ×40): presence of diffusely distributed histiocytes throughout the smears with vacuolated cytoplasm (fig. 1A,B)
- High power examination (×100): histiocytes with single, double, or multiple nuclei, fine chromatin and prominent basophilic nucleoli, abundant cytoplasm containing several intact plasma cells or lymphocytes, defined as emperipolesis (fig. 1C,D), and an occasional...
halo around the phagocytized cells (fig. 1E). These cytological confirmed RDD.

Histology (fig. 2) provided a definitive diagnosis of RDD with emperipolesis (fig. 2A), and immunohistochemical staining revealed positivity for S-100 protein and CD 68 (fig. 2B,C).

All other laboratory results were normal. The ESR (erythrocyte sedimentation rate) was 32 mm/h. Serology for hepatitis B and C viruses and syphilis, were negative. This asymptomatic patient has been diagnosed with HIV-positive 10 months prior to attending our clinic, with a CD4 cell count of 610 cells/μL and a viral load of 150,000.
copies of RNA/μL. At the time of RDD diagnosis, the chest radiograph, and the computed tomography scan of the thorax and abdomen were normal. He had no signs of vital organ compression or airway obstruction, so his condition was monitored (he did not receive any treatment) and re-examined at 4 and 6 weeks after the diagnosis. The size of the patient’s lymph nodes had not significantly increased at those follow-up examinations, and he was subsequently lost to follow-up.

**Discussion**

Rosai Dorfman disease was first described in 1969, and it is a rare nonmalignant histiocytic disorder that affects all age groups, including pediatric and elderly patients [5, 6]. Its etiology is still unknown. Infection and immunodeficiency have been suggested as causes of RDD. Relationships between RDD and HHV6, Epstein–Barr virus, klebsiella, and cytomegalovirus have been suggested, but attempts to isolate those organisms in patients diagnosed with RDD have consistently failed [10–12]. To date, no microorganism has been definitively incriminated as the causative agent of RDD. RDD is very rarely associated with HIV infection, with <10 cases having been reported to date. To the best of our knowledge, this case is the eighth to be reported. A summary of the sites of involvement, cytological features, histological features, and the treatments/courses of RDD cases with such an association are presented in Table 1 [13–18].

The main clinical manifestation of RDD is massive, bilateral, and painless cervical adenopathy, and extranodal disease is common. The sites of involvement in order of frequency are the cervical, axillary, inguinal, para-aortic, and mediastinal lymph nodes. Extranodal manifestation of the disease is observed in 28–43% of patients, with the head and neck region being the most common site affected [20]. The most common clinical presentation of the eight reported cases of RDD associated with HIV (75%) was the mixed form (nodal and extranodal involvement). Our case is the only one reported to have the typical RDD presentation.

The diagnosis of RDD can be difficult, as the patient may not have the classic features associated with nodal disease, such as fever, leukocytosis, and elevated ESR. Our patient did not have fever and had a WBC = 7.8G/L and an ESR = 32 mm/h. Lymphadenopathy cases with and without HIV infection are caused by Hodgkin disease, lymphoma, metastatic carcinoma, Langerhan’s cells histiocytosis, chronic infection etc.

The differential diagnosis of extranodal RDD varies according to the involvement site. If the lesions or lymphadenopathy persist, fine-needle aspiration or tissue biopsy is indicated.

The cytological features of RDD include the presence of intact lymphocytes, specifically, histiocytes containing plasma cells and a single nucleus or multiple nuclei of different sizes and shapes, inconspicuous to prominent nucleoli, and an abundantly pale cytoplasm. Less often, the cytoplasm contains neutrophils and red blood cells. Sometimes a halo can be observed around phagocytized cells. This phenomenon is called emperipolesis [7, 16, 18, 20, 21]. It differs from phagocytosis in that the cells that are taken up in the lesion are not attacked by enzymes and remain intact within the cytoplasm.

Histology shows dilated sinuses with numerous histiocytes that exhibit emperipolesis. Immunohistochemical features include positivity for S100 protein and CD68, and negativity for CD1a [13, 15, 17, 19]. These cytologic and histologic findings, which were found in our patient, are characteristic of RDD and essentially present in all RDD cases, regardless of the sites of involvement (nodal or extranodal) and regardless of the type of infection or associated pathology.

To date, there is no ideal treatment for RDD. Some patients experience spontaneous resolution. Surgery is performed for symptomatic cases, including cases with airway compression, vital organ compression, or cosmetic issues especially in cutaneous RDD cases. Other treatment modalities, such as chemotherapy, corticosteroids, and radiotherapy, have been performed with variable results [12, 15, 16, 19]. In patients with RDD and HIV infection, different treatment modalities have been used according to the site of involvement with variable outcomes. Only case number 5 (Table 1) died and that patient was an infant with CMV EOD (end-organ disease) complicated by bone marrow failure [17]. Based on the currently available data, we do not believe, that patients with asymptomatic HIV infection are more vulnerable to developing RDD. However, more studies must be undertaken to determine the role of HIV in the pathogenesis and/or its course of RDD.

Our case was followed for 6 weeks after diagnosis, and the size of the patient’s lymph node remained stable. After 6 weeks, he was lost to follow-up.

**Conclusion**

Rosai Dorfman disease is a very rare, benign, self-limiting histioproliferative disorder. Its cytologic features are so distinctive that it can be easily diagnosed by FNAC (fine-needle aspiration cytology), which is minimally invasive. If the lesions are accessible by fine needle aspiration, a biopsy may not be necessary.

Rosai Dorfman disease has rarely been described to be associated with HIV, and it is not known whether HIV infection contributes to the development of an environ-
Table 1. Rosai Dorfman disease associated with HIV infection.

| Cases | Authors, Year | Age/Sex | Lesion location | Serology | FNA cytological findings | Histology | Treatment/Course | References |
|-------|---------------|---------|----------------|----------|--------------------------|-----------|----------------|------------|
| 1     | Delacretaz, 1991 | 31/F    | Generalized lymphadenopathy: cervical, submaxillar, axillary | EBV, HHV6, HSV1/2, CMV: negative | – | Large histiocytes, emperipolesis. SP100 + /CD68-/Alpha-1-antichymotrypsin + | Excision/Follow-up | [13] |
| 2     | Perry, 1998   | –/–     | Skin, nasal nodules | HHV6+ EBV Ig G+ | – | Emperipolesis SP100+ CD68 weak CD1a - | Topical steroids/improvement at 2 months | [14] |
| 3     | Pitamber, 2003 | 28/F    | Skin: multiple erythematous papule, face | EBV + CMV + HBV+ | – | Pale histiocytes, emperipolesis. SP100+ CD68+ | Subtotal maxillectomy | [15] |
| 4     | Dickson-Gonzalez, 2007 | 56/F | Maxillar, malar | ? | Emperipolesis | | | |
| 5     | Nastouli, 2009 | Infant/F | Skin, liver, spleen, kidneys | CMV+ | – | Foamy histiocytes, SP100+ CD68+ Methylprednisolone/Temporary improvement/Death | | [16] |
| 6     | De Khurajam, 2012 | 40/M | Cervical lymph node, left parotide | ? | Emperipolesis | | | |
| 7     | Monroe, 2014  | 49/M    | Eye, retroperitoneal mass, axilar lymph node | HSV- VZV- CMV- | – | Emperipolesis SP100+ | Topical and oral Corticosteroids/rapid improvement | [17] |
| 8     | Our Case      | 19/M    | Cervical lymph node | HBV - STS - | Emperipolesis | | | |

M, male; F, female; HIV, human immunodeficiency virus; HHV-6, human herpes virus 6; HSV, herpes simplex virus; EBV, Epstein-Barr virus; VZV, virus varicella zona; CMV, cytomegalo virus; STS, serological tests for syphilis.
ment that stimulates macrophage activation. Therefore, the possible association between RDD and HIV should be more thoroughly studied.

Conflict of interest
None declared.

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