Clinicopathologic Characteristics of Rosai–Dorfman Disease in a Medical Center in Northern Taiwan

Cheng-Hsiang Hsiao,1,2 Tsen-Fang Tsai,3 Ting-Hua Yang,4 Chia-Ming Liu4*

Background/Purpose: Rosai–Dorfman disease (RDD) is a rare histiocytic proliferative disorder that usually presents as cervical lymphadenopathy. Extranodal involvement occurs in up to 40% of patients. The disease is most prevalent in blacks and rare in Asians. This study analyzed the characteristics of RDD in patients from Taiwan.

Methods: Fourteen patients with a diagnosis of RDD were identified by review of records from 1995 to 2004 at National Taiwan University Hospital. Tissue sections from each patient were reviewed and immunohistochemical staining was performed. Data on clinical presentations, associated diseases, treatment and outcome were analyzed. In situ hybridization for Epstein–Barr virus (EBV)-encoded small RNAs (EBER-1) was also performed. Sets of primers specific for the conservative region of bacterial 16S-rDNA, IS6110 of Mycobacterium tuberculosis complex and consensus region of human herpes virus (HHV) DNA polymerase genome were used to detect the presence of these infectious agents in the specimens.

Results: There were six men and eight women with a mean age of onset of 44 years. Nine patients presented with skin lesions, four with lymph node involvement and one with nasal tumor. All lesions followed a chronic and indolent course. Most of the lesions regressed spontaneously, and no patients died as a result of this disease during follow-up. Three patients had associated immune-mediated disease, i.e. hemolytic anemia, ankylosing spondylitis and asthma. Two patients had a history of tuberculosis. Histologically, all lesions were characterized by a mixed infiltrate of large pale histiocytes, abundant plasma cells and lymphocytes regardless of the site of involvement. The strong immunoreactivities of these histiocytes to S-100 protein, CD68 and CD14 with occasional lympophagocytosis were helpful in confirming the diagnosis, polymerase chain reaction analysis of 16S-rDNA, IS6110 and HHV gene and in situ hybridization for EBV were all negative.

Conclusion: RDD in Taiwan is characterized by older age of onset compared to Western countries (44 years vs. 20 years) and more frequent extranodal involvement. The skin was the most common site of extranodal involvement, with about two-thirds of patients presenting with cutaneous lesions. There was no evidence of bacterial, mycobacterial or HHV infection in this series. [J Formos Med Assoc 2006;105(9):701–707]

Key Words: lymphadenopathy, lymphophagocytosis, Rosai–Dorfman disease

Rosai–Dorfman disease (RDD) is a benign histiocytic proliferative disorder. Clinically, the disease is characterized by the presence of massive lymphadenopathy mostly involving the cervical lymph nodes.1 Histologically, the sinuses of the involved lymph nodes are distended by numerous distinctive histiocytes. These histiocytes are large and contain vesicular nuclei, distinct nucleoli and voluminous

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pale cytoplasm, often with lymphophagocytosis. In the beginning, the disease was thought to be confined to the lymph nodes and was thus initially named sinus histiocytosis with massive lymphadenopathy. With increasing study of this disease, however, it became evident that extranodal involvement is not uncommon. Therefore, the term sinus histiocytosis with massive lymphadenopathy is now no longer used to describe the disease, and RDD is considered more suitable for describing its presentation with extranodal involvement. Although RDD was first identified more than 30 years ago, most of the reported cases have been from the United States and Western Europe. A disproportionate but high number of cases have been reported from Africa and the Caribbean region, and only a few reports have been from Asia.

This study reviewed the characteristics of 14 cases of RDD diagnosed during the 10-year period from 1995 to 2004 in a single hospital in Taiwan, including clinical presentations, associated diseases, histologic findings and outcomes.

Methods

RDD was diagnosed in 14 patients during the 10-year period from 1995 to 2004 at National Taiwan University Hospital, a medical center in northern Taiwan. Information collected by chart review included demographic characteristics, clinical presentations, laboratory examinations, course and treatment regimens. Tissue samples in formalin-fixed and paraffin-embedded blocks were collected from the archive of the department of pathology at the same hospital. Routine hematoxylin and eosin staining of the recut sections were reviewed. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue using the avidin–biotin technique on an automatic immunostainer (BenchMark, Ventana Medical Systems Inc., Tucson, AZ, USA). Antibodies against CD20 (L-26, pan-B marker) (1:100; DAKO, Carpinteria, CA, USA), CD1a (Langerhans’ cell marker) (1:40; DAKO), S-100 protein (predominant reactivity in Langerhans’ cell) (1:400; DAKO), CD3 (pan T-cell marker) (1:100; DAKO), CD14 (lipopolysaccharide receptor on the surface membrane of macrophages) (1:40; Novocastra), CD15 (myeloid marker) (LeuM1, 1:50; DAKO), CD68 (KP-1, macrophage marker) (1:100; DAKO) and CD123 (expressed mainly in macrophages such as plasmacytoid dendritic cells) (1:40; BD PharMingen, Franklin Lakes, NJ, USA) were used. In situ hybridization for Epstein–Barr virus (EBV)-encoded small RNAs (EBER-1) was also performed on formalin-fixed, paraffin-embedded tissue sections. DNA extracted from paraffin-embedded tissue sections was used for polymerase chain reaction (PCR) analysis. Sets of primers specific for the conservative region of bacterial 16S-rDNA, IS6110 of Mycobacterium tuberculosis complex or consensus region of human herpes virus (HHV) DNA polymerase genome were used to detect the presence of these agents in the specimens.

Results

The 14 patients included six men and eight women, with ages ranging from 18 to 68 years (mean, 44 years). All lesions followed a chronic and indolent course. The duration from the onset of disease to diagnosis varied from 2 months to 4 years. Out of the 14 patients, 10 underwent resection or incisional biopsy only without further treatment, and four patients received medical treatment due to extensive lesions or the presence of residual lesions. No patients died of the disease during the study period. Nine patients had cutaneous or soft-tissue lesions. All of the cutaneous lesions presented as nodules or plaques with discoloration of the skin (Figure 1A). Two of the nine patients also had lymphadenopathy in addition to the skin lesions, but the nature of lymphadenopathy was unknown because no surgical specimen was taken from these lymph nodes. Four patients had nodal involvement of RDD confirmed by histologic examination and all of them presented with neck lymphadenopathy.
Only one patient presented with a mass lesion in the nasal cavity and paranasal sinuses (Figure 1B). Three patients had immunologic disorders including asthma, hemolytic anemia and ankylosing spondylitis. Two patients had tuberculosis many years before the onset of RDD. The clinical characteristics of each patient are shown in the Table.

Histologically, all lesions showed mixed inflammation comprising histiocytes, plasma cells, lymphocytes and some neutrophils. At low-power examination, a characteristic pattern of alternating pale and dark areas was seen in most specimens (Figure 2A). The clear area was composed of histiocytes with a polygonal shape and abundant eosinophilic to clear cytoplasm and medium to large vesicular nuclei. The dark area contained numerous plasma cells and lymphocytes. Lymphophagocytosis by the histiocytes, also called “emperipolesis”, was present to a variable degree in all lesions (Figure 2B). In nodal RDD, the characteristic histiocytes filled dilated sinuses, and the capsule was thickened and fibrotic (Figure 2C). In cutaneous lesions, inflammation was mainly located in the mid-dermis. The overlying epidermis was not remarkable, presenting without acanthosis and spongiosis.

Immunohistochemically, the infiltrating histiocytes were strongly reactive to S-100 protein (Figure 3), CD14 and CD68 but negative to CD1a, CD15, CD21 and CD123 in all specimens. The ingested lymphocytes within the histiocytes were either CD3 positive T-cell or CD20 positive B-cell. Plasma cells were also occasionally seen within the histiocytes. No sections contained EBER-1 transcript. PCR analysis for bacterial 16S-rDNA, IS6110 of M. tuberculosis complex and consensus region of HHV DNA polymerase genome were negative in all specimens.

Discussion
RDD was first reported by Rosai and Dorfman in 1969.3 It usually presents as massive, painless, neck lymph node enlargement. Clinically, RDD follows a chronic and indolent course. In studies from Western countries, most cases occurred during the first or second decade of life with a mean age of 20 years.4 In this study, the mean age at disease onset was 44 years, which is much older than that in studies reported from Western countries. The disorder is often self-limiting and subject to spontaneous regression. As such, most patients do not require therapy other than resection of the affected tissue. However, some patients with extensive or progressive disease may require further treatment.7 In this series, 10 of 14 patients underwent excisional biopsy or surgical resection only without further treatment, and most residual lesions regressed spontaneously but slowly. In the remaining four patients with extensive or multiple lesions, different therapeutic regimens were attempted, and most lesions regressed. However, no definite conclusion concerning the responses to each treatment could be derived due to limited information. No patients died of the disease in the follow-up period regardless of the modality of treatment.
**Table.** Clinical and laboratory findings, treatment and outcome of 14 patients with Rosai–Dorfman disease in Taiwan

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/ Sex</th>
<th>Clinical presentation</th>
<th>Laboratory findings</th>
<th>Associated clinical conditions</th>
<th>Duration</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/F</td>
<td>Multiple skin lesions over the extremities Right neck mass</td>
<td>EBV study ND Polyclonal gammopathy</td>
<td>Hemolytic anemia Tuberculosis diagnosed 12 yr previously</td>
<td>4 yr</td>
<td>Prednisolone Hydroxychloroquin Anti-CD20</td>
<td>Partial response</td>
</tr>
<tr>
<td>2</td>
<td>25/F</td>
<td>Scalp tumor</td>
<td>EBV study ND</td>
<td>Nil</td>
<td>6 mo</td>
<td>Resection</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>3</td>
<td>19/F</td>
<td>Left neck mass*</td>
<td>EBV IgG: 1:640 (+)</td>
<td>Asthma Chronic ulcer</td>
<td>2 mo</td>
<td>Resection</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>4</td>
<td>68/M</td>
<td>Multiple skin nodules Axillary lymphadenopathy</td>
<td>Direct Coomb test (+) EBV study ND</td>
<td>Nil</td>
<td>2 yr</td>
<td>Isotretinoin Roaccutane</td>
<td>Lost F/U</td>
</tr>
<tr>
<td>5</td>
<td>18/M</td>
<td>Multiple pigmented skin lesions over the abdomen and extremities</td>
<td>EBV IgG: 1:2560 (+)</td>
<td>Ankylosing spondylitis RDD diagnosed in younger brother 2 yr before</td>
<td>3 yr</td>
<td>Prednisolone</td>
<td>Regression after treatment for 6 yr</td>
</tr>
<tr>
<td>6</td>
<td>58/M</td>
<td>Bilateral neck mass*</td>
<td>EBV study ND</td>
<td>Nil</td>
<td>3 mo</td>
<td>Resection of left LN</td>
<td>Lost F/U</td>
</tr>
<tr>
<td>7</td>
<td>23/F</td>
<td>Skin lesions over the left flank and deltoid areas</td>
<td>EBV study ND</td>
<td>Nil</td>
<td>2 yr</td>
<td>Biopsy</td>
<td>Lost F/U</td>
</tr>
<tr>
<td>8</td>
<td>61/M</td>
<td>Left thigh lesions</td>
<td>EBV study ND Polygammopathy</td>
<td>Nil</td>
<td>4 yr</td>
<td>Resection</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>9</td>
<td>35/F</td>
<td>Right shoulder plaque</td>
<td>EBV study ND</td>
<td>Nil</td>
<td>2–3 mo</td>
<td>Dapson</td>
<td>Lost F/U</td>
</tr>
<tr>
<td>10</td>
<td>33/F</td>
<td>Hyperpigmented skin lesions on trunk</td>
<td>EBV study ND</td>
<td>Tuberculosis diagnosed 15 yr previously</td>
<td>11 mo</td>
<td>Biopsy</td>
<td>Partial spontaneous regression</td>
</tr>
<tr>
<td>11</td>
<td>53/F</td>
<td>Right neck mass*</td>
<td>EBV study ND</td>
<td>Nil</td>
<td>2 mo</td>
<td>Resection</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>12</td>
<td>53/M</td>
<td>Nasal tumor paranasal and sacral involvement</td>
<td>EBV IgG: 1:1930 (+)</td>
<td>Nil</td>
<td>1 yr</td>
<td>Resection of nasal tumor</td>
<td>Partial spontaneous regression</td>
</tr>
<tr>
<td>13</td>
<td>58/M</td>
<td>Right neck mass*</td>
<td>EBV study ND</td>
<td>Nil</td>
<td>2 mo</td>
<td>Resection</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>14</td>
<td>61/F</td>
<td>Left thigh nodules</td>
<td>EBV study ND</td>
<td>Nil</td>
<td>1 yr</td>
<td>Biopsy</td>
<td>Partial spontaneous regression</td>
</tr>
</tbody>
</table>

*Lymph node involvement of Rosai–Dorfman disease was confirmed by lymphadenectomy. EBV = Epstein–Barr virus; ND = not done; F/U = follow-up.*
Up to 40% of cases have extranodal lesions in the studies from Western countries. Skin, nasal cavities, paranasal sinuses, soft tissue and orbits are the most common sites of extranodal RDD. In a 423-case study of RDD by Foucar et al., 49 cases (11.6%) had skin involvement, and one-fourth of them had lymph node involvement simultaneously. In this study, out of 14 patients, 10 (71.4%) had extranodal involvement, of which nine presented with cutaneous lesions and only one presented with nasal tumor. Two of the nine patients with cutaneous RDD also had lymph node enlargement, but the nature of the enlarged lymph node was unknown. The etiology of the high prevalence of extranodal involvement and predominant skin manifestation of RDD in Taiwan is unclear. Similar observations were also reported by Lu et al.3

Clinically, cutaneous RDD usually presents as erythematous or brownish infiltrated nodules or plaques with surrounding satellite papules. This must be differentiated from sarcoidosis, deep fungal infection, tuberculosis cutis and other
cutaneous histiocytosis. The skin of the entire body can be involved by cutaneous RDD.\textsuperscript{10,11} The trunk and extremities were the most commonly involved sites in our study (8/9) and in two other serial studies. In contrast, the head and neck were the most frequently affected sites in the study by Lu et al.\textsuperscript{5}

Histologically, RDD has characteristic features regardless of the site involved. Full-blown lesions are characterized by a mixed, florid infiltrate of large pale histiocytes, abundant plasma cells and lymphocytes. These morphologic features may lead to confusion with other diseases with histiocytic infiltration such as fungal infection, mycobacterial infection and inflammatory pseudotumor. Cutaneous RDD may also be confused with xanthomatous lesions such as xanthogranuloma, fibrohistiocytoma and xanthoma.\textsuperscript{2,12} Immunohistochemical staining is useful in differentiating RDD from these histiocytic lesions. The histiocytes of RDD are thought to be activated macrophages derived from circulating monocytes, and they are usually strongly reactive to CD68 (a macrophage marker), CD14 and S-100 protein. CD14 is a lipopolysaccharide receptor expressed on the membrane of macrophages. In contrast, the histiocytes of xanthomatous lesions are positive for CD68 but negative for S-100 protein. RDD may also be confused with Langerhans’ cell histiocytosis because Langerhans’ cells also express S-100 protein.\textsuperscript{13} However, the nuclei of Langerhans’ cells are characterized by the presence of nuclear grooving, which is rarely seen in RDD cells. In addition, Langerhans’ cells are reactive to CD1a, but RDD histiocytes are not.\textsuperscript{14} Emperipolysis, ingestion of lymphocytes by histiocytes, is found to a variable degree in all lesions. The ingested lymphocytes could be B-cells or T-cells.\textsuperscript{15} In late or treated cutaneous RDD, the number of histiocytes decreases. Thus, it is difficult for the pathologist to make a correct diagnosis at this stage. In this situation, S-100 protein stain is able to highlight the characteristic histiocytes and confirm the diagnosis.\textsuperscript{2} Although the etiology of RDD remains unknown, infectious agents have been suspected to be the cause of the disease because fever and pharyngitis precede its onset in some patients. Various investigations, including routine and special cultures of oropharynx or excised tissue, skin tests, serology, electron microscopy and special histochemical stains, have been used to determine the possible infectious agents associated with RDD; however, they all failed to show direct evidence of specific microorganisms.\textsuperscript{4} In this study, we used sets of primers specific for the bacteria 16S-rDNA, IS6110 of \textit{M. tuberculosis} complex, and the consensus region of HHV DNA polymerase gene to analyze the DNA extracted from pathologic specimens. No PCR product of these infectious agents could be found in any of the specimens. A significant number of patients with RDD had antibodies to HHV-6 or EBV.\textsuperscript{16} Serologic study for EBV was performed in three patients in this series, and all showed elevated EBV IgG, but no EBV genome was detected in the tissue sections by \textit{in situ} hybridization. The absence of herpes viral genome using PCR analysis in this study further confirms that EBV seropositivity is more of an epiphenomenon of abnormal immune response, which is not unusual in patients with RDD.

Various immune disorders have been reported to be associated with RDD, among which hemolytic anemia and arthritis are the most common.\textsuperscript{17} Other immunologic disorders such as asthma and juvenile onset of diabetes mellitus have also been reported. Thirteen percent (56/423) of patients in Foucar et al’s\textsuperscript{5} series had immune-associated disease. Three patients (21.4\%) in this study had immunologic dysfunction including asthma, hemolytic anemia and ankylosing spondylitis. Two of them also had elevated serum EBV IgG titer. The cause of the association between RDD and autoimmune disease is unclear. Recently, Maric et al\textsuperscript{18} reported that histologic features of RDD could also be found in the lymph nodes of some patients with autoimmune lymphoproliferative syndrome (ALPS). The latter is an inherited disorder associated with defects in Fas-mediated apoptosis, characterized most often by childhood onset of lymphadenopathy, splenomegaly, hypergammaglobulinemia and autoimmune phenomena. Some cases of RDD,
particularly those with autoimmune disease, may be associated with heritable defects in Fas-mediated apoptosis and have overlap symptoms with ALPS.¹⁸

Two of our patients had a history of tuberculosis at 15 and 12 years before the onset of RDD, respectively. These two patients were cured after a complete course of antituberculous treatment. Foucar et al¹⁴ reported severe streptococcal pneumonia in six patients in a registry of 423 patients with RDD, but no tuberculosis was found in their study. The reason for the development of tuberculosis preceding the onset of RDD in the two patients is unknown; the higher prevalence of tuberculosis in Taiwan and underlying immune defect could both have played a role.

Familial RDD was reported in four families including two twins and two siblings. An 18-year-old male patient (case 5) in this study also had familial RDD. His younger brother also had RDD involving the neck lymph node diagnosed in another hospital 2 years before the development of cutaneous RDD. The familial occurrence of RDD suggests that the disease may be transmitted through close contact.

In summary, this study found that the biologic features of RDD in Taiwan are not significantly different from those in Western countries, although there are still some differences in presentation. First, the age of onset of RDD in Taiwan (44 years) is older than that in Western countries (20 years). Second, extranodal involvement is more common than pure nodal involvement, and the skin is the major site of involvement.

References