Rosai-Dorfman Disease With Central Nervous System Involvement

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Introduction

Rosai-Dorfman disease is a rare benign disease that was first described by Rosai and Dorfman as sinus histiocytosis with massive lymphadenopathy in the 1960s.[1] This disorder is documented in all age groups, but adolescents are noted to be most affected.[2] The usual presentation of this disorder includes cervical lymphadenopathy, which is chronic and self-limiting. Lymphadenopathy is massive, and is associated with a raised erythrocyte sedimentation rate, anemia, pyrexia, and polyclonal hypergammaglobulinemia.[2] Skin, orbital, and central nervous system (CNS) involvement are rare manifestations. Slightly more than one-third of cases present with extranodal manifestations.[2] We present 3 cases of Rosai-Dorfman disease: 1 with progressive CNS involvement and 2 with disease limited to the cervical lymph nodes.

Case Reports

Case 1

A 6-year-old African American boy was seen in the Pediatric Ear, Nose, and Throat clinic with decreased hearing, poor vision, nasal stuffiness, and cervical lymph node enlargement. He was confirmed to have sinus histiocytosis with massive lymphadenopathy by biopsy and extensive clinical, radiologic, and immunologic studies. Extensive disease was evident in his maxillary sinuses bilaterally. Computed tomography (CT) scans showed extensive involvement in the neck and maxillary sinuses, but the CNS was free of disease. He was treated with vinblastine and prednisolone, which resulted in marked resolution of the lymphadenopathy. He also underwent surgery for marsupialization of the mass in his left maxillary sinus. While the maxillary sinus mass remained static, his disease progressed in the CNS, with extension of the meningeal infiltrate to the cortex and spine (Figures 1 and 2). He was given external beam radiotherapy (XRT) to the head and spine and treated with chemotherapy, including interferon, cyclosporine, methylprednisone, VP16, and vinblastine. Although his magnetic resonance imaging (MRI) was drastically abnormal, he continued to lead a relatively normal life, complicated by very poor vision, loss of hearing, seizures, and psychologic problems, and with radiologic evidence of extension of the disease to all parts of the CNS, including the spine. The patient's mother refused any further therapeutic trials and signed a "Do Not Resuscitate" order. The patient survived until 19 years of age, but died after Hurricane Katrina while being evacuated to another state.

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Case 2

A 5-year-old boy presented with massive cervical lymphadenopathy. There was no history of weight loss, fever, or night sweats. Biopsy of cervical nodes confirmed sinus histiocytosis (Figure 3). There was no other site of disease, and bone marrow was not involved. The child did not receive any therapy and did well for 5 years, after which he was lost to follow-up.

Case 3

A 17-year-old African American boy presented to us with a history of progressive bilateral cervical lymphadenopathy for 3 years. There was no history of fever, weight loss, or night sweats. On examination, several large, firm, nontender nodes (as large as 7–8 cm) were noted bilaterally in the neck. There was no evidence of generalized adenopathy or organomegaly. MRI showed the adenopathy pushing the bases of both tonsillar beds and extending into the cervical region. Lymph node biopsy confirmed the diagnosis of sinus histiocytosis (Figure 4). He was treated with vinblastine (6.5 mg/m^2) and prednisone (40 mg/m^2) for 6 months, and the adenopathy regressed remarkably. The patient did

Table 1. Summary of Cases

	Case 1	Case 2	Case 3
Age (years)	6	5	17
Sex	M	M	M
Race	African American	African American	African American
Primary Site	Maxillary sinus and cervical nodes	Cervical nodes	Cervical nodes
Additional Site	Orbit, CNS (spine and intracranial)	None	None
Complications	Poor vision, hearing loss, seizures, psychosocial issues	No clinical problems except mass	Mild tracheal compression
Treatment and Prognosis	Vinblastine, VP-16, cyclosporine, prednisone, XRT	No treatment. Unchanged clinical status for 5 years Lost to follow-up	Vinblastine, prednisone, recurrence after 8 months (no further treatment, no change for 3 years)

CNS=central nervous system; VP-16=etoposide; XRT=external beam radiation therapy.

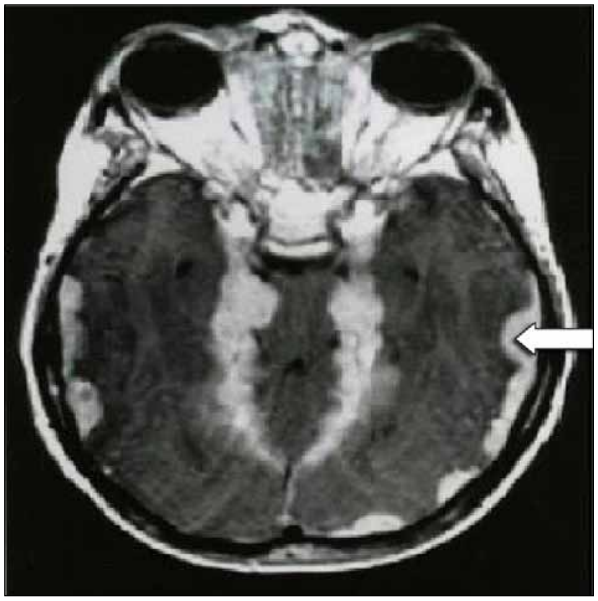

Figure 1. Postcontrast, T1-weighted, axial magnetic resonance imaging showing diffuse meningeal infiltration (arrow).

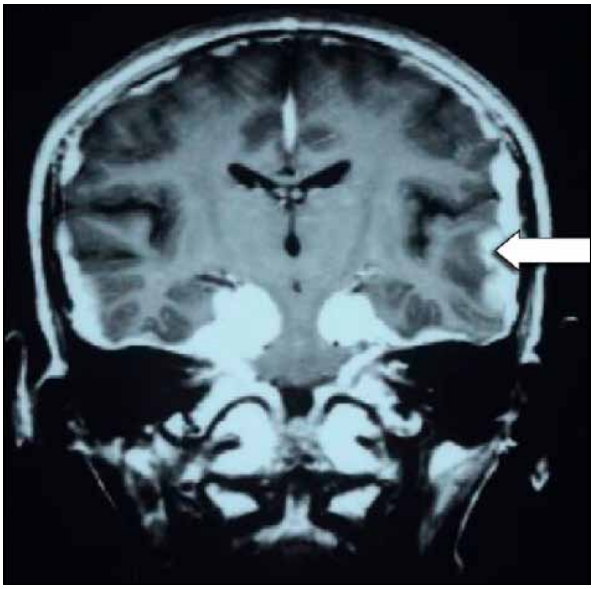

Figure 2. Postcontrast, T1-weighted, coronal image showing meningeal infiltration (arrow).

well for a year post-therapy, but the cervical nodes recurred and repeat biopsy showed sinus histiocytosis again. Since he was asymptomatic, no further treatment was suggested. He continued to do well without any problems for 3 years and was transferred to adult oncology care.

Discussion

Rosai-Dorfman disease is a rare disorder with unknown etiology. There are few cases linking pathogenesis to immunologic and lymphoproliferative disorders. Usual presentation of this disorder includes cervical lymphadenopathy, which is chronic and self-limiting. Lymphadenopathy is massive and associated with raised erythrocyte sedimentation rate, anemia, pyrexia, and polyclonal hypergammaglobulinemia.[2] In addition to the cervical lymph nodes, the nose, mouth, and upper gastrointestinal tract are other usual sites.[3-6] Skin, orbital, and CNS involvement are rare manifestations. Characteristic histologic features of sinus histiocytosis with massive lymphadenopathy (SHML) are large histiocytes with abundant eosinophilic cytoplasm, which also contain numerous phagocytosed lymphocytes.[7] In addition to the usual aforementioned histologic features, tissue fibrosis is also common in extranodal cases of SHML.

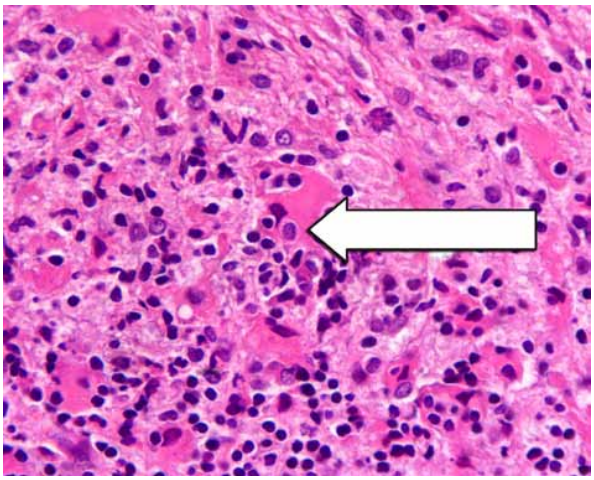

Figure 3. Cervical lymph node biopsy slide. The sinus mucosal biopsy had histiocytes with abundant eosinophilic cytoplasm, often with hematopoietic cells within cytoplasmic vacuoles with little evidence of cellular breakdown within the histiocytes. The histiocytic nuclei were often round and vesicular, with a central nucleoli (arrow). Others had pyknotic-appearing nuclei with collapsed, featureless hyperchromatic chromatin with irregular nuclear outlines (hematoxylin and eosin stain, 600X).

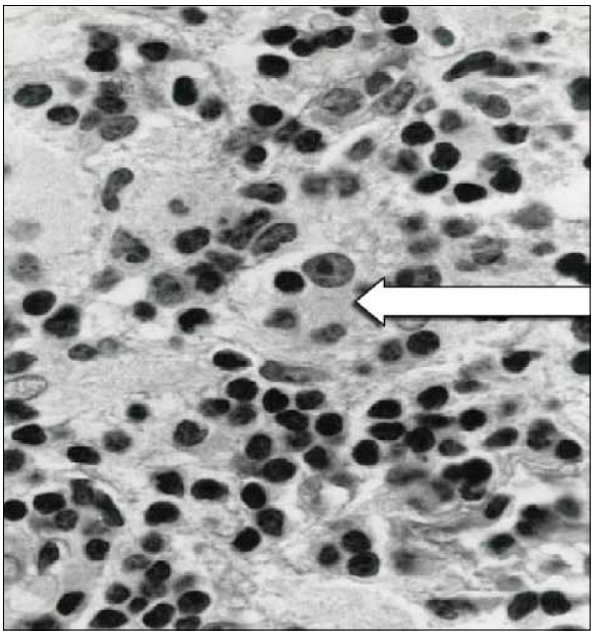

Figure 4. Cervical lymph node biopsy slide. Immunohistologic stain for S100 performed to confirm the diagnosis.

The rarity of SHML with the presence of progressive CNS disease in children has prompted us to present this case series. Extranodal involvement, especially of the CNS, can cause a diagnostic dilemma. There has not been any systematic study of SHML, and treatment does not appear to be necessary in the majority of cases. Treatment modalities including surgery, chemotherapy, and radiation have been used with no clear demonstration of response.[8-11] The typical reason for treatment with radiation, surgery, or chemotherapy was threatened loss of function due to spinal cord compression or respiratory embarrassment. Even at high doses, the responses are inferior to that expected with malignant hematopoietic disease. Most patients with SHML do not require specific therapy. Ideal treatment for those with extensive or progressive disease has not been identified. The responses seen in our patients to regimens effective for hematopoietic malignancies have not been dramatic or sustained. Recent literature does show some positive results with alternative therapies. In a single case, 2-chlorodeoxyadenosine (2-CdA) was successfully administered when the conventional treatment failed.[12] The use of imatinib (Gleevec, Novartis) is slowly becoming more widespread, as indicated by the latest literature.[13,14] A recent case report also suggests rituximab (Rituxan, Genentech) for the treatment of Rosai-Dorfman disease.[15] Nevertheless, more studies on pathogenesis and other treatment modalities are required.

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Review

Rosai-Dorfman Disease: Management of CNS and Systemic Involvement

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Juan Rosai and Ronald Dorfman were the first to recognize sinus histiocytosis with massive lymphadenopathy (SHML) as a distinct clinicopathologic entity.[1] They described SHML as a benign proliferation of distinct histiocytes in the sinuses of lymph nodes or the lymphatics of extranodal sites. To better understand this rare disorder, with an estimated incidence of 100 cases per year in the United States, they established a registry that provided a great deal of insight into the clinical features and natural course of this disorder.[2] Because of their contribution, SHML is now often referred to as Rosai-Dorfman disease (RDD), particularly when referring to extranodal presentations of this disease.

Warrier and colleagues[2] present 3 cases of RDD in pediatric patients. All 3 patients presented with cervical lymphadenopathy, which is the most common presenting symptom. Approximately 90% of patients with RDD present with lymphadenopathy, and most of these involve the cervical lymph nodes. Approximately 43% of cases also have extranodal involvement, with 75% of the extranodal disease involving the head and neck, but any organ system can be involved. The average age of presentation for RDD is approximately 20 years, with many children and young adults affected.[1,3] Most patients with RDD have an excellent prognosis with eventual spontaneous resolution of their disease. However, the clinical course of RDD is variable; it can be either relapsing-remitting or progressive, and the outcome relates to clinical location as well as treatment response. Patients with an unfavorable course tend to have disseminated nodal disease, involvement of multiple extranodal sites, immunologic abnormalities, or involvement of the kidney, liver, or lower respiratory tract.[3]

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Diagnosis

Because RDD can involve almost any organ system, the clinical presentation can vary widely. In addition to lymphadenopathy, patients with RDD can present with fevers (28%), weight loss (9%), malaise (4%), or night sweats (2%). There is no association with sex, and RDD seems to be less common in those of Asian descent. RDD is associated with immune disorders in approximately 15% of patients. The most common immune disorder is autoimmune hemolytic anemia, but polyarthritis, rheumatoid arthritis, glomerulonephritis, asthma, and juvenile onset diabetes can also be present. Common laboratory abnormalities include polyclonal hypergammaglobulinemia (91%), elevated erythrocyte sedimentation rate (89%), and anemia (66%). Less common laboratory abnormalities include rheumatoid factor, antinuclear antibodies, and a reversal of the CD4/CD8 ratio in peripheral lymphocytes.[3]

Tissue sampling is required for pathologic diagnosis; often a fine needle aspiration (FNA) is adequate and should be attempted first.[4] If nondiagnostic or cytologic yield is insufficient for necessary staining, a biopsy may be required. In involved lymph nodes, RDD histocytes can be seen accumulating in the sinusoids with an infiltrate of plasma cells and small lymphocytes, in some cases distorting the architecture of the lymph node. RDD histiocytes characteristically demonstrate emperipolesis, defined as the presence of intact cells within their cytoplasm, which distinguishes this process from phagocytosis. The intact cells are most commonly lymphocytes, but may also be plasma cells, neutrophils, or red blood cells.[2,5] RDD cells express both macrophage and dendritic cell antigens, and are therefore CD14- and CD163-positive (macrophage markers) as well as S100- and CD68-positive (both macrophage and dendritic cell markers) and fascin-positive (dendritic cell marker). Unlike Langerhans cell histiocytosis (LCH), RDD histiocytes are CD1a-negative. Extranodal sites of involvement often exhibit the same histologic features, but tend to have more fibrosis, fewer RDD histiocytes, and less emperipolesis.[3]

Pathogenesis

Since RDD was first described over 40 years ago, the mechanism behind this disease has not been discovered. As it is not associated with a monoclonal cell population, RDD is not considered a malignancy, and it is thought that infectious or immunologic causes may be responsible. Early efforts in determining the pathogenesis of RDD focused on viral causes. After 2 cases of RDD were reported in the literature with elevated Epstein-Barr virus (EBV) titers, several studies evaluated the presence of EBV in RDD histiocytes and found no evidence of EBV by in situ hybridization (ISH) and polymerase chain reaction (PCR).[6,7]

The human herpesvirus (HHV)-6 has been investigated as a causative agent of RDD in several studies, with mixed results. One study found HHV-6 DNA in involved histiocytes by in situ DNA hybridization in 7 of 9 patients with RDD, and another study demonstrated HHV-6 protein in the late phase of the viral cycle in histiocytes of 2 patients with RDD.[8,9] However, another report of 3 patients with cutaneous RDD found elevated HHV-6 IgG in 1 patient and no evidence of HHV-6 DNA by PCR.[10] In light of these findings and because HHV-6 is commonly present in lymphoid tissue, the role of HHV-6 in the pathogenesis of RDD remains unclear.

Parvovirus B19 and polyomavirus have also been evaluated as causative agents in RDD. Parvovirus B19 is associated with inflammatory and autoimmune diseases, and the capsid proteins VP1 and VP2 were found in the lymphocytes of 4 RDD cases by immunohistochemistry (IHC). However, the parvovirus B19 capsid proteins were also found in the respiratory epithelium and not in the histiocytes of RDD.[11] Another series evaluated 19 patients with soft tissue RDD and found that 3 of 9 abdominal cases were positive by IHC for cytoplasmic and nuclear simian virus 40 (SV40), which is known to be carcinogenic.[7] The antibody used in this study did have some cross reactivity with the large T antigen of the BK virus (another polyomavirus), which is associated with hemorrhagic cystitis. The significance of this finding is unclear and the relationship of RDD to viral causes has not been confirmed.

More recent efforts in elucidating the pathogenetic mechanisms of RDD have focused on investigating rare inherited disorders that present with lymphadenopathy and are associated with RDD. Autoimmune lymphoproliferative syndrome (ALPS) is a rare disorder that was first described in 1967 and presents in childhood with nonmalignant lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, and autoimmune manifestations.[12] ALPS results from defects in the apoptotic pathway mediated by Fas and Fas ligand. The failure of lymphocytes to undergo apoptosis in patients with ALPS results in the accumulation of these lymphocytes, leading to lymphadenopathy and hepatosplenomegaly. An expanded population of mature T-cell lymphocytes that are CD4- and CD8-negative is characteristic of ALPS, and the increased number of autoreactive lymphocytes is thought to account for the autoimmune manifestations of this disease. The majority of ALPS cases are associated with mutations in the *TNFRSF6* gene that encodes the Fas protein, but other cases are associated with mutations in the genes encoding caspases 8 and 10 or unknown mutations.[12,13] One study evaluated lymph node biopsies from 44 patients with ALPS and mutations in the *TNFRSF6* gene and found histologic features of RDD in 18 of these patients. The tissue from 14 patients with sporadic RDD was then obtained to sequence the *TNFRSF6* gene, but the tissue was only adequate in 4 patients for gene sequencing. None of the 4 patients with sporadic RDD had mutations on sequencing.[12]

Another inherited syndrome, Faisalabad histiocytosis (FHC) has more recently been associated with RDD. FHC is an autosomal recessive disorder that presents with joint deformities, sensorineural hearing loss, and lymphadenopathy that is histologically similar to RDD. Mutation analysis was performed on 1 family with FCH and 2 families with familial RDD. A genome-wide linkage scan confirmed linkage at chromosome 10q22.1 and direct sequencing revealed mutations in *SLC29A3* in all 3 families. The *SLC29A3* gene encodes an intracellular nucleotide transporter (hENT3) with wide tissue distribution that localizes to the mitochondria and has an affinity for adenosine.[14] The exact mechanism of this mutation in producing the phenotypic manifestations of FHC and familial RDD is unknown, but hENT3 could alter the apoptotic pathway by altering adenosine metabolism. It is unknown if mutations in *SLC29A3* are present in cases of sporadic RDD, and this is an area for future study.

Although the exact mechanism leading to RDD has not been determined, much progress has been made in recent years through the study of familial RDD and other rare inherited syndromes such as ALPS and FHC. Viral mechanisms have been studied, but convincing evidence of a viral case for RDD has not been found to date. Based on familial cases, RDD may result from defects in apoptosis, but more study is needed to determine the specific mutations in the majority of sporadic cases. If specific genetic defects are found, targeted therapy can be developed to treat RDD in those patients with systemic involvement or symptomatic lesions.

CNS Involvement

Involvement of the central nervous system (CNS) in RDD is not common, and occurs in approximately 5% of patients. However, CNS involvement does not portend a worse prognosis. Patients with CNS involvement tend to be older, with a median age of 39 years, and are almost 2 times more likely to be male.[15] Presenting symptoms vary greatly with the location, size, and number of lesions and can include seizures, headaches, endocrine abnormalities, or focal neurologic deficits, such as visual changes, weakness, or loss of sensation. In the registry published in 1990, half of the 21 patients with CNS disease had lymphadenopathy and two-thirds had other sites of extranodal disease.[2] More than 100 cases of CNS RDD have now been reported in the literature and more than two-thirds of these cases have isolated intracranial disease.[15] It is possible that many

cases of isolated CNS RDD in the past were diagnosed as another entity without other evidence of systemic RDD to help confirm the diagnosis.

In the CNS, RDD most commonly presents as a dural-based intracranial mass, but cases of intraparenchymal RDD have been reported as well.[16] Close to 90% of patients with CNS RDD have intracranial lesions, but dural-based lesions in the spinal canal can also occur and typically present with spinal cord compression resulting in paraplegia.[2,16,17] A case of an intramedullary RDD spinal cord lesion has also been reported.[17] Approximately one-fourth of patients with CNS RDD will have multiple CNS lesions. Because the majority of cases are dural-based, meningioma is the most common preoperative diagnosis. However, CNS RDD can also mimic subdural hematoma, ependymoma, and Lhermitte-Duclos disease.

On computed tomography (CT), CNS RDD lesions will appear isointense or hyperintense, homogenous, and will enhance with contrast administration, but they will not contain calcifications. On magnetic resonance imaging (MRI), RDD lesions appear homogenous and isointense on T1-weighted images and heterogeneous with areas of isointensity and hypointensity on T2-weighted images.[18,19] On diffusion-weighted and apparent diffusion coefficient (ADC) map images, CNS RDD will typically appear isointense, but some hyperintensity on diffusion-weighted images is possible.[19] RDD lesions will have homogeneous enhancement with the administration of gadolinium and will typically have a dural tail. Perilesional edema is commonly seen on both CT and MRI.[18,19]

Surgical resection is preferred in the management of CNS RDD to relieve neurologic symptoms and provide a diagnosis. If a gross total resection (GTR) is performed, the risk of relapse is low and no other therapy is needed.[16] In many cases, complete removal of the CNS RDD is not possible due to the location, and subtotal resection (STR) is performed to provide a diagnosis and improve symptoms. If neurologic symptoms resolve after STR, then observation is a reasonable approach, as the majority of CNS RDD lesions will remain stable after STR.[16,17] If neurologic symptoms persist after STR or there is concern for further deterioration due to the location of the lesion, then adjuvant therapy should be considered. Fractionated radiotherapy, stereotactic radiotherapy, corticosteroids, and chemotherapy have all been used in the treatment of CNS RDD, and the optimal management is unclear at this time. Corticosteroids after STR have resulted in the complete resolution of CNS RDD.[20] If neurologic symptoms persist after surgery, or resection is not possible, then fractioned radiotherapy (typical doses, 20–30 Gy at 2 Gy/fraction) or stereotactic radiosurgery (12 Gy 50% isodose line has been used) can be considered.[21,22] Not all lesions have responded to radiotherapy, but details on dose and fractionation are not available in all cases, so it is difficult to determine the optimal dose and fractionation. Methotrexate-based chemotherapy regimens have been used as well with some response, and may be beneficial in cases of incompletely resected CNS RDD that have not responded to corticosteroids or radiotherapy.[23]

Systemic Treatment

In the registry published in 1990, 20% of patients with RDD and at least 1 year of follow-up had complete resolution of their disease and 70% had persistent but stable disease. The remaining 10% had progressive disease or died from RDD or other causes.[3] Because of the rarity of RDD, no clinical trials have been undertaken to evaluate treatment strategies, and observations must be made from reported cases. In patients with RDD involvement of lymph nodes or extranodal sites outside of the CNS, treatment should be reserved for patients with symptomatic lesions or involvement of vital organs. With this approach, only half of patients with RDD will require treatment.[24] Patients who develop a fever of higher than 38°C without evidence of infection and those who have rapidly enlarging lymphadenopathy should be given a course of corticosteroids. At least 1 case of RDD that was resistant to prednisone resulted in a complete response to dexamethasone, and this should be considered when selecting corticosteroid therapy.[25] Surgical excision, radiotherapy, or both may be considered for RDD that involves vital organs.

Many different systemic agents have been used in RDD with mixed success. Vinca alkaloids, anthracyclines, and alkylating agents obtained a response in 2 of 12 patients in 1 review. The 2 patients who responded both received 6-Mercaptopurine (6MP) and methotrexate.[24] Other therapies that have been used include imatinib (Gleevec, Novartis), rituximab (Rituxan, Genentech), 2-chlorodeoxyadenosine (2-CdA), and interferon-α. Imatinib, a multi-kinase inhibitor of *BCR-ABL*, *PDGFRA*, *PDGFRB*, and *KIT*, produced a complete response in a patient with multi-organ involvement of RDD whose histiocytes were positive for *PDGFRB* and *KIT*. [26] Another patient with cutaneous RDD did not respond to imatinib therapy, but in this case the RDD histiocytes were positive for *PDGFRA* but not *PDGFRB* or *KIT*.[27] Rituximab, a monoclonal antibody to CD20, has produced a complete response in 3 patients with RDD and immunologic symptoms.[28-30] 2-CdA, a purine analog, has been used in at least 6 cases, with a complete reponse in 4, a partial response in 1, and no response in the last case.[31,32] Finally, high-dose interferon-α has been used with complete response in at least 1 patient.[33]

High-dose chemotherapy has not produced significant responses in RDD; newer therapies such as rituximab, 2-CdA, imatinib, and interferon-α may be of benefit and should be the focus of future investigation. As more is learned about the pathogenesis of RDD, therapies targeted to specific defects may prove to be of benefit. Patients with immunologic manifestations may benefit from therapies targeted to the immune system, such as rituximab.

Conclusion

RDD is a rare, nonmalignant, histiocytic disease that presents in children and young adults with lymphadenopathy or extranodal proliferation of distinctive histiocytes. CNS RDD can occur, and the majority of cases are isolated to the CNS and managed with surgical excision. CNS RDD does not portend a worse prognosis, and diffuse lymphadenopathy or extranodal involvement are associated with an increased risk of progression and death. The mechanisms behind RDD are currently unknown, but the association with immunologic abnormalities indicates a possible immunologic or inflammatory cause. No specific viral cause has been found, but studies of patients with ALPS and FHC with RDD have demonstrated a possible link to defective apoptotic signaling. Further studies should determine if these same abnormalities are present in cases of sporadic RDD. As more is discovered about the pathogenesis of RDD, treatment can be further refined. Immune modulators such as rituximab may play a growing role in the treatment of RDD, particularly in patients with immunologic abnormalities.

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