

Rosai-Dorfman Disease

Introduction

Rosai-Dorfman disease (RDD) is a rare histiocytic disorder initially described as a separate entity in 1969 by Rosai and Dorfman under the term sinus histiocytosis with massive lymphadenopathy (SHML) (1). The causes of RDD are not fully understood, and treatment strategies can be different according to severity or vital organ involvement.

Epidemiology/Etiology

Although RDD may occur in any age group, it is most frequently seen in children and young adults (2). Patients presenting with isolated intracranial disease tend to be older (3). The disease is more common in males and in individuals of African descent (4). RDD has been reported following bone marrow transplant for precursor-B acute lymphoblastic leukemia (5), and concurrently or after Hodgkin's and non-Hodgkin's lymphoma (6). A cytokine-mediated migration of monocytes may be involved in histiocytes accumulation and activation. This functional activation could be triggered by different stimuli, due to the coexistence of RDD and autoimmune diseases, hematological malignancies and post-infectious conditions. In fact, many viruses like Herpesvirus 6 (HHV-6) (7) and Epstein-Barr virus (EBV) (8) have been implicated as potential causative agents, however, there is no strong evidence for this at the moment.

Pathology

Histologically, lymph nodes show pericapsular fibrosis and dilated sinuses, heavily infiltrated with large histiocytes, lymphocytes and plasma cells. The presence of emperipolesis, or the engulfment of lymphocytes and erythrocytes by histiocytes that express S-100, is considered diagnostic of RDD although not uniquely. Apart from S-100 antigen positivity, immunohistochemical stains of RDD cells are also positive for CD68, CD163, α_1 -antichymotrypsin, α_1 -antitrypsin, fascin and HAM-56 while CD1a is typically negative (2). RDD lesions have a moderate expression of IL-6, which could be related to the associated polyclonal plasmacytosis and hypergammaglobulinemia. Furthermore, the lesions tend to express strongly IL-1 β and TNF- α . Systemic symptoms in RDD may be related to enhanced production of these cytokines (9).

Clinical features

The most frequent clinical presentation of RDD is a massive bilateral and painless cervical lymphadenopathy with fever, night sweats and weight loss. Mediastinal, inguinal and retroperitoneal nodes may also be involved. Extranodal involvement by RDD has been documented in 43% of cases with the most frequent sites being skin, soft tissue, upper respiratory tract, multifocal bone, eye and retro-orbital tissue with lymphadenopathy or as an isolated initial manifestation of disease (10). Other reported sites include urogenital tract, breast, gastrointestinal tract, liver, pancreas and lungs. Head and neck involvement has been reported in 22% of cases, most commonly the nasal cavity followed by the parotid gland (2). Intracranial RDD usually occurs without extracranial lymphadenopathy, and most intracranial lesions are attached to the dura with only few extending intraparenchymally. CNS disease can present clinically and radiologically as meningioma, but the presence of emperipolesis in the CSF is usually

diagnostic of Rosai-Dorfman disease (11). More recently, RDD cases presenting with initial spine, kidney, thyroid, isolated mediastinal and unifocal skeletal involvement have been reported (12-15). Histologically, the disease must be differentiated from Langerhans cell histiocytosis (LCH), infectious and lymphoproliferative disorders (3), as well as sinus hyperplasia. S-100 positivity can usually distinguish between the latter condition and RDD, whereas in both conditions the histiocytes have a strong macrophage antigen expression (16)

Laboratory features in RDD are often non-specific. Leukocytosis, elevated sedimentation rate and polyclonal gammopathy have been reported in most patients. Normochromic/normocytic and autoimmune hemolytic anemia and elevated serum ferritin have also been described (10,17). Skeletal lesions of RDD are typically osteolytic and can be confused radiographically with LCH (10). Fludeoxyglucose F-18 positron emission tomography (PET) scan was found to be sensitive indicator for early prediction of treatment response in patients with systemic RDD (18).

The clinical course of RDD is unpredictable with episodes of exacerbation and remissions that could last many years. The disease is often self-limiting with a very good outcome, nevertheless 5-11% of patients die from their disease. RDD patients can be subdivided into three categories: 1) patients with only lymph nodes that enlarge suddenly with spontaneous regression and without any further recurrences; 2) patients with immunologic abnormalities at presentation who have a more widespread nodal disease and a higher fatality rate (10,19); 3) patients with several extranodal site involvement, multinodal disease and a protracted clinical course with multiple relapses and remissions for years. In these cases, the severity of disease depends on the type and number of extranodal sites (4).

Cutaneous Rosai-Dorfman disease (C-RDD) is a distinct entity from systemic RDD, confined to the skin without lymphadenopathy and with different demographic features (20). Skin lesions are usually papules or nodules that are firm, indurated ranging in size from 1 to 10 cm. Pustular, psoriasiform and acneiform presentations have also been documented (21). C-RDD has a benign course usually with spontaneous regression in most cases. Therapy may be needed for relapsed cases and for cosmetic reasons only.

Treatment

In the majority of cases, RDD has a benign course and treatment is not necessary. Therapy is required, however, for patients with extranodal RDD having vital organ involvement or those with nodal disease causing life-threatening complications (22). Surgery is generally limited to biopsy, but debulking may be required in patients with vital organ compromise such as intracranial dural-based lesions (3) or upper airway obstruction (22). When complete resection has excessive morbidity then partial resection with adjuvant radiosurgery can be successful (23). Surgical excision of resectable lesions induced complete remission (CR) in 8 out of 9 patients (22). Radiotherapy has limited efficacy in most cases, although one recent report showed benefit in a refractory orbital RDD with visual disturbances (24). Systemic corticosteroids are usually helpful in decreasing nodal size and symptoms, however they can be quite immunosuppressive and recurrence of RDD lesions can occur after a short period of interruption (25). Prolonged

course of low-dose prednisone was very effective in a case of RDD with skin and lymph nodal involvement with respiratory obstruction (26).

Results with chemotherapeutic agents have not been encouraging, and it is possible that different patients with RDD may respond to different drugs. Antimetabolite therapy with low-dose methotrexate (MTX) and 6-mercaptopurine (6MP) was effective in only 2 out of 10 patients, one of them had previously failed etoposide and corticosteroids (27). Another series showed some benefit in a few patients after a combination of MTX/6MP/vinblastine/6-thioguanine. Anthracyclines, alkylating agents and vinca alkaloids have limited efficacy, although some benefit with vinblastine has been reported. (22). Prolonged therapy with Interferon- α was successful in two case reports (28,29), although another study showed failure of interferon plus chemotherapy (22). Treatment with acyclovir (30) and with thalidomide (31) caused CR in 2 single case reports. A recent case report described a patient with RDD who showed a rapid and complete response to the tyrosine kinase inhibitor imatinib. The patient's histiocytes were positive for the imatinib target proteins platelet-derived growth factor-receptor β (PDGFRB) and KIT. The disease completely responded to treatment with 400-600 mg daily of imatinib for more than 7 months (32). Drugs that specifically target cytokines (TNF- α and IL-6), such as cladribine (or 2-CDA), have been found to be effective in recurrent, refractory or severe cases of RDD (33-35). Furthermore, the efficacy of the anti-CD20 monoclonal antibody/rituximab has been described in one case (36).

Therapy Recommendations

Patients with RDD without vital organ involvement should be followed closely without any active therapy. Patients with systemic symptoms or those with sudden enlargement of nodes may be treated with prolonged course of low-dose prednisone; the optimal duration of this is yet to be defined. For patients with vital organ compression, surgery and high-dose corticosteroids should be tried first, but radiotherapy may be needed in resistant cases or whenever surgery is not feasible.

Since RDD is self-limited in most patients, the use of chemotherapy should be restricted to patients with life-threatening disease or in non-responsive and/or multiply relapsing cases. Combination therapy with low-dose MTX & 6MP seems justifiable in patients with multiple reactivations or major cosmetic problems. Patients with severe RDD and those with refractory/relapsed disease might benefit from treatment with single-agent 2-CDA. The use of new drugs like imatinib should be tested in the context of a clinical trial. Further understanding of the biology of this rare disease, in addition to the development of international clinical trials might lead to novel and more effective treatment strategies.

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