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Review

A Mini-Review of Ocular and Periocular Rosai-Dorfman Disease: A Masquerading Pathology with Unknown Etiology

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ABSTRACT

Rosai-Dorfman disease (RDD) is a rare sub type of non-Langerhans cell histiocytosis with a predilection for the head and neck that specially involve cervical lymph nodes. Classic histopathologic features include emperipolesis and Immunohistochemical stains are strongly positive for S-100 and CD68 but negative for CD1a in most cases. The exact nature and RDD etiology remains unknown. More than 40% of RDD patients show extra nodal involvements. Ophthalmic manifestations can be detect in 10% of all patients in which, the highest prevalence is related to orbital lesions. In the presence of orbital and intraocular lesions, systemic involvements are more likely to be associated. There is no specific treatment for this disease therefore, treatment modalities should be individualize based on site of involvement and presence or absence of systemic involvement.

Keywords: Emperipolesis; Orbital mass; Rosai-Dorfman disease; Eye; Lymphadenopathy

INTRODUCTION

Rosai–Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare disorder of unknown etiology that Patients usually present with cervical lymphadenopathy after a brief, nonspecific febrile illness [1,2].

Rosai–Dorfman disease is a systemic disorder described in detail in 1969 by two pathologists, Juan Rosai and Ronald Dorfman, followed by their name [1]. This non-malignant histiocytic disorder has special histopathologic features of abundant histiocytes, engulfed lymphocytes and lymphoid cells and often demonstrating emperipolesis [1].

Characteristic signs of the disorder are lymph nodes involvement and bulging in the area of the head and neck, but 43% of patients present with extranodal involvements, mostly in skin, bone, upper respiratory tract, ocular and Periocular tissue [2]. About 10 % of patients have ocular and periocular findings. Ophthalmic manifestations include orbital mass, scleritis, corneal lesion, uveitis, choroidal mass and even lacrimal duct obstruction [3-13]. The aim of this mini-review is to provide the latest information on epidemiology, pathophysiology, diagnosis, and treatment of RDD.

METHOD

The authors conducted a literature search of available sources describing the issue of Rosai-Dorfman Disease with special focus on RDD ocular and periocular manifestations.

EPIDEMIOLOGY

The first reports of RDD were mostly in the African American population and subsequent studies revealed that this disease has no specific predilection for geographic location or race. The disorder can affected individuals of any age, but most often affects young adults. The average age of onset is approximately 20 years however, some older patients can be affected by this disorder [1-3].

No clear familial inheritance pattern has been recorded and the disease has a male preponderance. It is estimated that there are fewer than 100 cases of RDD in United States each year [2]. The prevalence for ocular and Periocular RDD is not clear and has been reported from 2.3% of all orbital lesions to 0.09% of all ophthalmic specimens in one tertiary referral center [6].

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Received: January 5, 2021; **Accepted:** January 22, 2021; **Published:** January 30, 2021

Citation: Masoomia B, Haghbin A, Ghodous S (2021) A Mini-Review of Ocular and Periocular Rosai-Dorfman Disease: A Masquerading Pathology with Unknown Etiology. Lupus: Open Access. 6:163.

ETIOLOGY AND CAUSE

The exact cause of Rosai-Dorfman disease is unknown (idiopathic), but it does not seem to be of neoplastic group. Researchers have suggested that the disorder may be caused by an infectious agent, immunodeficiency, or autoimmunity. Many infectious agents have also been hypothesized as the cause of RDD, including cytomegalovirus, parvovirus B19, varicella zoster virus, bacterial (Klebsiella) or an aberrant response to an unspecified antigen such as Human Herpes Virus 6 (HHV-6). Interestingly, hemolytic anemia has been reported in RDD patients and parvovirus B19 is a frequent cause of this finding [15]. However, studies investigating these agents have been unrevealing [7-15].

Some recent reports showed MAP/ERK pathway alterations in a group of RDD patients, which suggests that at least a subset, may be neoplastic in nature [16]. The presence of characteristic histiocytes derived from circulating mononuclear cells, long history of disease and the presence of high serum auto reactive antibodies during active disease, suggests a possible pathogenic correlation with an immune dysregulatory process [7].

CLINICAL PICTURE

The clinical features of RDD may vary from benign soft tissue masses or lymphadenopathy to life threatening compression of vital organs, anaemia, or leukopenia [2]. RDD is a chronic disease with episodes of exacerbation and remission. Foucar et al reported progressive disease in only 1%, spontaneous regression in 21%, and stable disease in 78% of patients [2]. This disease is a benign self-limiting illness that mostly present with brief febrile illness, pharyngitis and joint pain [2-17]. Massive, bilateral, painless cervical Lymphadenopathy and elevated erythrocyte sedimentation (ESR) rate, are the most prominent features seen in approximately 90% of cases. The other lymph node regions such as axillary, inguinal, and paravertebral areas can be involved in 30% of patients [2-17]. Unlike other histiocytic disorders, there is a notable lack of hepatosplenomegaly [2]. Also, RDD is characterized by an abnormal proliferation of histiocytes within subcapsular and medullary lymph nodes sinuses but, in 40% of cases extra nodal site can involve that include nasal cavity/paranasal sinuses (16%), skin and soft tissue (16%), bone (11%), ocular and periocular tissue (10%) salivary gland (7%), central nervous system (7%) kidney/genitourinary tract (3%), and respiratory tract (3%) [2]. Involvement of the kidney and /or lung has been found to be a poor prognosis outcome [2,3].

Ocular and periocular involvement may be the initial or principal manifestation of the disease [2-13]. Approximately 20% of all ophthalmic cases had no evidence of lymphadenopathy but, many had another site of extranodal involvements, most frequently the nasal cavity and/or paranasal sinuses [2-13]. RDD Patients may also present with decreased visual acuity, diplopia, orbital pain, ptosis, eyelid thickening or retraction and strabismus. Other ophthalmic manifestations include epibulbar (conjunctival) masses, uveitis, scleritis, serous retinal detachments, perilimbal lesions with or without corneal involvement, and naso-lcrimal duct obstruction [2-13]. Foucar et al, reviewed a large series of 423 documented RDD patients in which 36 (8.5%) cases had ocular and periocular involvement including orbit (n=26), eyelid (n=5), uvea (n=4), and conjunctiva (n=1). They showed orbital involvement may manifest years before associated lymphadenopathy [2]. Interestingly, eyelid , orbit and conjunctival lesions, has been found to have no specific effect on prognosis, but RDD intraocular manifestations (e.g. choroidal lesions and/or uveitis) have been associated with aggressive disease and an unfavorable prognosis [2-13]. Chio et al reported 4 RDD cases with intraocular involvement (Uveitis, scleritis, retinal detachment and ciliary body mass) and noted that they all demonstrated multi-organ disease, including lymph nodes, sinusitis, renal and lung involvement [3]. Unlike orbital and intraocular involvement, perilimbal lesions can be present without systemic manifestations [13-21].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RDD is broad and it may mimic clinically some systemic conditions such as sarcoidosis, tuberculosis, leukemia, Wegener's granulomatosis, Hodgkin's lymphoma and many other neoplastic and inflammatory conditions. Intraocular lesions may confused with choroidal melanoma. Orbital involvement may have clinical features of slow onset lesions including orbital pseudotumor, metastatic disease, Lymphoma, juvenile xanthogranuloma (JXG), Erdheim-Chester disease, IgG4-related sclerosing disease and even optic nerve tumors [2-15]. Histopathologically, emperipolesis may be seen (rarely) in lymph nodes of other diseases such as salmonellosis, histoplasmosis or rhinoscleroma [15].

DIAGNOSIS

Definitive diagnosis of RDD must be based on histologic and immunohistochemical analysis after surgical biopsy or fine needle aspiration (FNA) [2,3]. The characteristic histopathology features are histiocytic infiltration admixed with lymphocytes and other inflammatory cells. Classically, there is a population of histiocytes displaying phagocytosed lymphocytes and plasma cells termed lymph phagocytosis or "emperipolesis" [2]. Emperipolesis is the strongest indicator of the diagnosis and is rare outside the setting of RDD [17]. Histiocytes may occasional atypical nuclear features, but mitotic figures are infrequent [17]. Extranodal sites (e.g. orbital lesions) can simulate lymph node architecture on histopathology sections but, they often demonstrate more prominent fibrosis and show a decrease in the number of emperipolesis cells [2].

Histiocytes in RDD, Langerhans cell histiocytoses (LCH), and other histiocytoses (e.g. xanthogranuloma) express S-100, a neural tissue specific protein. Furthermore, RDD tissue shows immunoreactivity for CD163, CD68, but in contrast to LCH, the histiocytes in RDD very rarely stain with CD1a and no ultra structural rod-shaped Birbeck (Langerhans) granules are present [7-19].

Establishing a definitive histologic diagnosis of RDD can be a difficult challenge even for experienced pathologist therefore, they will need immunohistochemical (IHC) tests. Compare to orbital lesions, in perilimbal and conjunctival masses or intraocular involvements , after biopsy, it is sometimes not

possible to view a classic RDD histology sample, therefore, the role of IHC tests would be very valuable [13].

TREATMENT

Optimal therapy for RDD is not well established and patient's management in RDD is individualized, and depends on the nature of the lesion tissue, involvement of adjacent structures, and volume of tumour disease. Foucar et al has documented that approximately 50% of patients require intervention including surgical excision, corticosteroids, chemotherapy, and radiotherapy and may be combinations of the above [2-19]. As explained before, in a group of patients the lesion regresses spontaneously. This suggests that there is a role for monitoring without therapy in a subset of RDD patients who are asymptomatic and have no internal organ involvement [18]. Complete Surgical excision or even debulking has been suggested as a curative option for some isolated and accessible masses whereas, some patients needs subsequent additional treatments [17-19]. In orbital and perilimbal lesions, excisional biopsy often shows curative results with low recurrence rate [13-21].

Corticosteroids have been shown to play a role in reducing symptoms and even treating lesions but, the optimal duration of therapy is unknown and the patients need to be monitored for the adverse effects from steroids [17,19]. Chemotherapy has been suggested for some patients with systemic involvements or sight threatening optic nerve compression [8-19]. Various drugs, such as alkylating agents (cyclophosphamide, Chlorambucil), antimetabolites (methotrexate, azathioprine), vinca alkaloids (vincristine, vinblastine), and others (e.g. doxorubicin, etoposide) have been used. The most successful responses were obtained with a combination of steroids, a vinca alkaloid and alkylating agents [7].

Prior reports suggested the potential role of radiation therapy in refractory disease causing imminent symptoms such as airway obstruction or vision loss secondary to orbital lesions [19]. Radiotherapy has been reported with doses range from 1000 to 5000 cGy. In Komp et al study, 10 of 34 (30%) patients with RDD that were treated with radiotherapy showed some improvement but only 1 patient achieved complete response [20].

Anti CD-20 monoclonal antibody, Rituximab has shown positive treatment response in some systemic RDD cases. The mechanism responsible for Rituximab response is unclear but, it may be due to inhibition of immuno-modulatory signals or indirect targeting of the precursor cells supporting the plasmacytic infiltrate [22].

PROGNOSIS

RDD has chronic nature with indolent course that cause morbidity more. An unfavorable prognosis has been found to correlate with increased in both number of nodal groups and the number of extranodal systems involvement [2]. RDD Mortality rates have approached 7% 2 that mainly belongs to patients with renal, lung or CNS infiltration [14]. Interestingly, examination of tissue samples of the deceased does not show malignant changes [14]. In RDD patients due to potential malignant transformation, systemic manifestations of RDD, or potential vision or life-threatening recurrences, it is vitally important to monitor patients for long time.

FUNDING

This research received no specific grant from any funding agency.

CONFLICT OF INTEREST

There was no special funder for this study and no conflicting relationship exists for any author. The manuscript has been read and approved by all the authors. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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