CASE REPORT

Cerebral Infiltrative Lesion and Chronic Clinical Course of the Rosai-Dorfman Disease

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Abstract

Rosai-Dorfman disease (RDD) is a rare disorder of an unknown etiology, characterized by a benign histiocytic proliferation in the lymph nodes, as well as the extranodal sites. Painless bilateral lymphadenopathy is the classic presentation of RDD in the majority of patients. The exteranodal disease involves the skin, soft tissues, bones, the genitourinary system, the lower respiratory tract, and the central nervous system.

A seven-year-old boy was referred to our hospital with left parietal swelling, headache, fever, imbalance, weight loss, and speech and walking impairments. In early examinations, he showed a hyposignal infiltrative lesion in the lateral ventricle and the choroid plexus, expanding to the subcortical white matter of the bilateral temporo-occipital areas. After surgery and sampling, he was diagnosed with cerebral RDD. According to his history, he had bilateral cervical lymphadenopathy at the age of two years, femoral soft tissue involvement at the age of three, and a skin disorder that improved with local treatments at the age of five. However, at the time of referral to the hospital, there were no other symptoms in other areas, except for brain symptoms.

In the differential diagnosis of brain lesions with specific borders in high-contrast radiological views, the probability of RDD should be considered, similar to meningioma. The presence of painless and extensive bilateral cervical lymphadenopathy can improve the diagnosis of this disease. Isolated brain involvement in RDD is very rare, and it can be seen in less than 5% of cases. Nevertheless, by early diagnosis and intervention, the risk of complications is reduced, and the prognosis is improved.

Keywords: Cerebral lesion; Histiocytic proliferation; Rosai-Dorfman disease
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Introduction

In 1965, Destombes reported a form of adenitis with lipid excess, occurring in children and young adults in the Antilles and Mali (1). The nodal form of this disease, also referred to as sinus histiocytosis with massive lymphadenopathy (SHML), was first described in 1969 (8). Later, the pioneering pathologists, Rosai and Dorfman, established and registered the clinicopathological entity of SHML and named it Rosai-Dorfman disease (RDD) (2).

Histiocytic disorders are classified into malignant/neoplastic and non-malignant types. Generally, RDD is a rare disorder of an unknown etiology, characterized by the non-malignant proliferation of histiocytes that can be located in the lymph nodes or the extranodal sites. Painless bilateral lymphadenopathy is the classic presentation of RDD in the majority of these patients (2). Although the etiology of RDD is not well-defined, some studies have associated RDD with viral infections (3) and somatic BRAF-V600E mutations (4). Also, recent studies have identified NRAS, KRAS, MAP2K1, and ARAF mutations in patients with RDD (6-10).

RDD occurs with a prevalence of 1:200, 000 worldwide and is reported to be less common in females and Asians, as compared to Caucasians and Africans. However, the cutaneous form of RDD is more frequently seen in children and young adults (mean age: 20.6 years), although it has been reported up to the age of 74 years (5). Histologically, emperipolesis (lymphocyte phagocytosis) or the presence of intact lymphocytes in histiocytes is a characteristic feature of SHML and RDD. The plasma cells, neutrophils, and red blood cells may be also found in the cytoplasm of histiocytes (10). The immunohistochemistry of histiocytes indicates high positivity for S100, CD68, HAM56, CD14, CD46, and CD15. In contrast to Langerhans cell histiocytosis (LCH), staining is rarely positive for CD1a in SHML (10). Extranodal involvements of the skin, soft tissues, bones, the genitourinary system, the lower respiratory tract, and the oral cavity have been reported in 43% of RDD patients. Also, RDD may be accompanied by lymphadenopathy, and multisystem involvement occurs in 19% of cases (11).

Bone involvement occurs in 5-10% of RDD cases, typically in the nodal form of the disease (12). Bone lesions commonly occur in the metaphysis and diaphysis of the femur or tibia, with soft tissue extension, which is either osteolytic or mixed lytic/sclerotic. RDD manifests in the central nervous system (CNS) only in 5% of cases. The high-risk period is between the second and sixth decades of life, with a mean age of 39.4 years at presentation (13). The courses of SHML and RDD are characterized by spontaneous resolution in most cases. Some patients may have episodes of exacerbation, alternating with periods of remission that continue for many years; however, the timing and duration of each phase are entirely unpredictable. Besides, the associated immune dysfunction leads to unfavorable outcomes (14).

Different treatment options have been proposed for RDD. However, only 50% of patients require treatment (10), as 20-50% of cases with a nodal/

cutaneous disease will have a spontaneous remission (15). Steroid therapy, radiation, different chemotherapeutic regimens, and TNF inhibitors have been used with low response rates. Today, there is not enough evidence to determine the prognosis of RDD, although it is more favorable in the lymphatic and cutaneous forms (16).

Case Report

A seven-year-old boy was referred to our hospital with left parietal swelling, headache, imbalance, fever, weight loss, and speech and walking impairments. His symptoms had started with headache three to four months earlier and intensified gradually. He was the first child of the family and had normal growth and development during infancy and childhood. The parents did not have a consanguineous marriage.

The patient had painless bilateral cervical lymphadenopathy when he was two years old and underwent antibiotic treatment, according to his medical history of an infectious disease. About seven months later, the lymph nodes diminished spontaneously, and no biopsy was taken from the lymph nodes. At the age of three, a soft tissue mass in the left lateral femur was observed with dimensions of 1.5×3 cm. After examination, a tumor was found in the vastus lateralis, with invasion to the perimuscular fascia and subcutaneous fat; therefore, surgical removal of the tumor was carried out. Also, the pathology results indicated a soft tissue tumor with benign fibrous histiocytoma. When the child was five years old, he presented with pruritus (a cutaneous rash) on the head, ears, and chest and was referred to a children's immunology clinic with suspicion of allergic reaction. Several tests, including immunoglobulin, complement, liver, and kidney tests, were performed, all of which indicated normal results. A pediatric immunologist started to treat the patient, based on a food allergy diagnosis. The skin lesions recovered after about four months, and no biopsy was taken. Concurrent with the skin lesions, behavioral changes appeared as restlessness and aggression, which were ignored. Finally, when the patient was seven years old, he was referred to the hospital with macrocephaly, prominent scalp arteries, and deterioration of verbal and motor skills. There was no pathological evidence in the complete blood count test, liver and kidney tests, lipid profile, and fibrinogen measurements; the erythrocyte sedimentation rate (ESR) was estimated at 10 mm/h. A dural-based tumor was found in the MRI of the brain and spine, with massive T1 isosignal and T2 hyposignal interventricular masses because of the involvement of the choroid plexus in the lateral ventricle invasion. Also, there was vasogenic edema, given the parenchymal involvement of the ventricle, besides the involvement of the upper sagittal sinuses in the posterior region. Accordingly, differential diagnoses, including Wegener's granulomatosis, LCH, sarcoidosis, tuberculosis, lymphoma, glioma, and metastatic lesions, were suggested (Figure 1).

Simultaneously, computerized tomography (CT) scan of the lungs, stomach, and hip was performed, which indicated normal results. In the eye retinoscopy, there was some evidence to support the high probability of chronic intracranial pressure. The patient was subjected to craniotomy, and the tumor was removed as much as possible; also, a ventriculoperitoneal shunt was implanted to reduce the cerebrospinal fluid pressure (Figure 2). The pathology result of the cerebral lesion indicated proliferation of histiocytotic cells with an almost huge eosinophilic cytoplasm, multinucleated

giant cells, and emperipolesis with infiltration of inflammatory lymphoplasma cells in an extremely fibrotic background with ischemic cores, a normal plexus choroid, and a brain gliotic tissue (without high mitotic activity, indicating an infectious organism). The final diagnosis of the patient was established as RDD.

The patient received treatment with corticosteroids and vinblastine, and radiotherapy of the central neural system was performed according to the RDD diagnosis, based on the cerebral involvement protocol. MRI was performed three months after treatment. The size of the dural-based tumor was enlarged scarcely, and evidence of subdural effusion and pachymeningitis was detected. The intraventricular tumor was removed after surgery and treatment; however, the side effects of radiotherapy were observed.

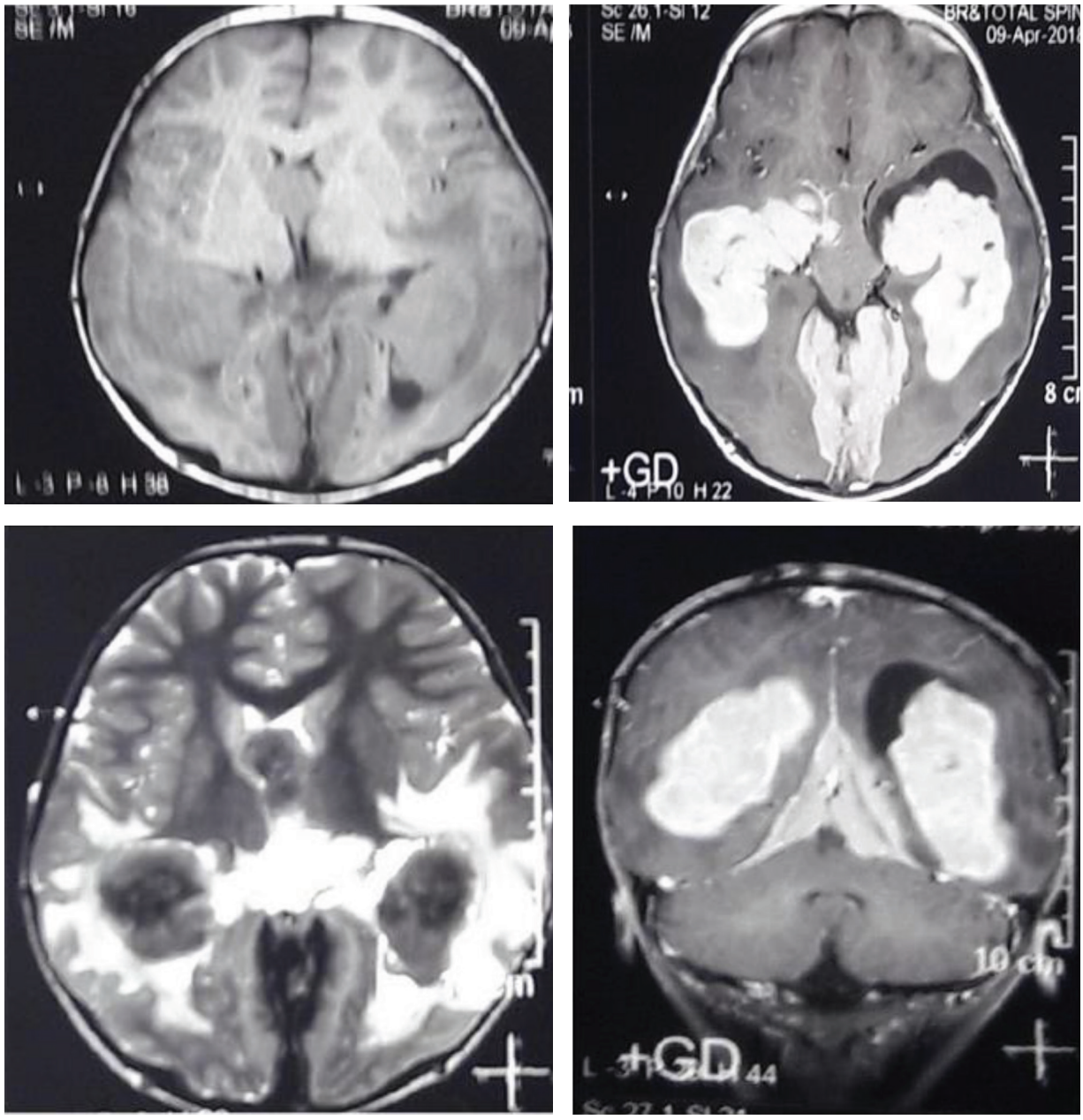

Figure 1. *Continues →*

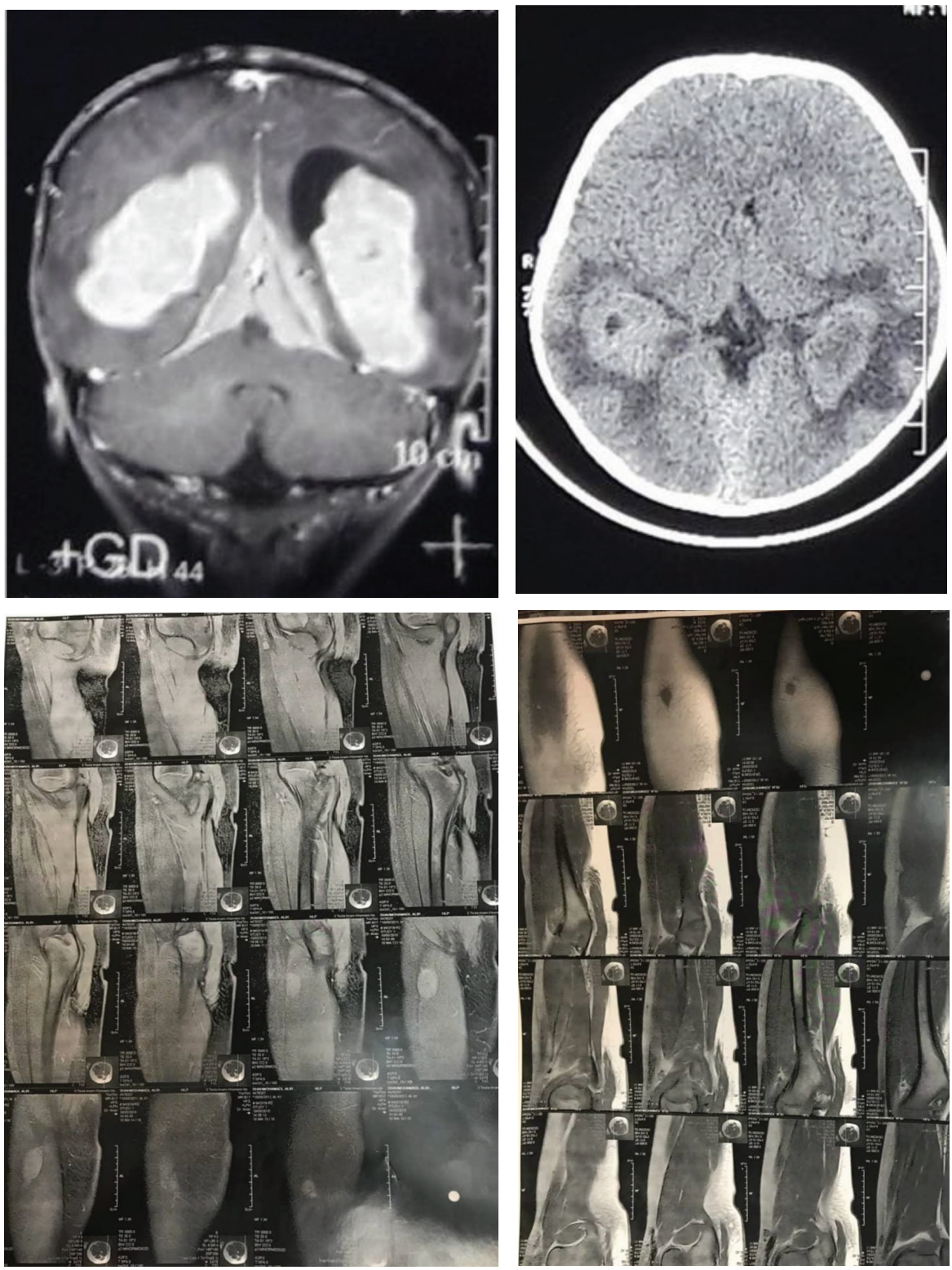

Figure 1. *The patient's brain MRI findings. There are mutilobulated intraventricular masses in the lateral ventricles, causing hydrocephalus and significant edema in the adjacent parenchyma. Another extra-axial dural-based mass, located in the tentorium, is also observed, encasing the posterior aspect of the superior sagittal sinus. The masses appear hyperdense on the CT scan, with low signal intensities on T1- and T2-weighted images; they also show avid contrast enhancement after contrast administration.*

Discussion

RDD was first described by Destombes in 1965 and was characterized as a distinctive clinicopathologic entity by Rosai and Dorfman in 1969 (17). This disease usually occurs in children and young men (mean age: 20.6 years) (17, 18). It is characterized by massive and painless bilateral cervical lymphadenopathy. The microscopic evaluation of lymph nodes revealed foamy histiocytes and plasma cells. In the immunohistochemical investigation, these histiocytes were found to be positive for S-100 and CD68 and negative for CD1a (18-20).

There are some hypotheses concerning the etiology of RDD. The histiocytes in RDD may be derived from stimulated macrophages. This stimulation may be affected by an uncommon reaction of the hematolymphoid system to an immune disorder. Some researchers have suggested viral involvements in this syndrome, as in in situ studies, the Epstein-Barr virus and human herpesvirus 6 were detected in some cases (18).

Extranodal RDD occurs in nearly 43% of cases (21-23). The most commonly affected sites include the orbit, the neck, the upper respiratory tract, the skin, bones, and testicles (18, 24). However, less than 5% of RD cases may occur in the CNS, with or without nodal involvement (17). Isolated intracranial RDD, without nodal involvement, is extremely rare. Intracranial RDD usually affects adult males in their fourth or fifth decade of life (mean age of 39.5 years that is insignificantly higher than nodal RDD) (20, 24). Commonly, it occurs as a dural-based solitary mass, similar to the present study. Although multiple lesions are uncommon, they have been described in some previous studies (17, 24). The commonly affected sites include the suprasellar region, the cerebral convexity, and the parasagittal region. The clinical presentations of this disease depend on the position of the tumor and may include headache, epilepsy, and cranial nerve disorders (18, 24).

Intracranial RDD is usually confused with meningioma in radiological diagnosis (24, 25). The same error was made in the present study, which is due to the similarity of dural-based masses. In T2-weighted MRI, meningiomas appear with low to high signal intensity (18). On the other hand, RDD is associated with hypointensity or isointensity on T1- and T2-weighted images and shows marked homogenous enhancement after contrast administration (25). LCH, lymphoma, metastatic carcinoma, melanoma, and granulomatous inflammation are other radiological differential diagnoses of intracranial RDD, besides tuberculosis and sarcoidosis (18, 24).

The accurate diagnosis of intracranial RDD is dependent on the results of histopathology and immunohistochemistry. Eosinophils are also involved in this condition. Langerhans histiocytes, when xanthomatous, may resemble histiocytes in RDD. Immunologically, both RDD and LCH are positive for S-100. Nevertheless, Langerhans cells have a folded nucleus with longitudinal grooves, absent in RDD histiocytes. Unlike RDD, the Langerhans histiocytes are positive for CD1a (21). Treatments that are widely accepted for RRD include surgery, corticosteroid therapy, chemotherapy, and radiotherapy (17, 18, 24). Surgical excision can be performed as the most effective treatment (24, 25). In the present study, surgical excision was not possible due to the extensive involvement of the adjacent structures in the tumor. The patient is now under corticosteroid treatment. Overall, RDD does not have a good prognosis, even if the disease is intracranial. In this regard, in a study by Andriko et al., nine out of 11 patients lived for 2-42

months (mean age: 15 months). No patient showed recurrence of the disease, even with subtotal resection (21).

In Conclusion

In the differential diagnosis of painless and massive bilateral cervical lymphadenopathy, especially when no microbial etiology is confirmed, there is a possibility of histocytotic RDD in all age groups, especially in the age group of <20 years. Considering the numerous presentations, intranodal and extranodal involvements, and simultaneous involvement of many systems, full clinical examination, laboratory investigation, and biopsy are essential. Also, in the pathology report, emperipolesis had a higher diagnostic value. Therefore, special attention must be paid to the CNS symptoms, and early diagnostic and therapeutic measures must be prioritized. In these cases, the possibility of brain involvement is high, and high-contrast radiographic lesions, similar to meningioma, are hypotense and clear with distinguishable borders. Early surgical interventions, steroid therapy, chemotherapy, and radiotherapy decrease the risk of complications and improve the patient's prognosis.

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Author's Contribution

Study concept and design: S.H.N.; collection of data drafting of the primary manuscript: M.K.H. and P.M.; and critical revision of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

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