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Rosai–Dorfman Disease – Five Years Retrospective Analysis from Tertiary Cancer Center

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Abstract

Aim: To study the pattern of presentation and management of nodal and extranodal primary RDD.

Methodology: From 2010 to 2015, eleven patients diagnosed with Rosai–Dorfman Disease (RDD) presented at our institute. Nine of them were analyzed as they received treatment at our center. We had five neck primaries, three intracranial and one cutaneous disease. Hematological, radiological, histopathological and immunohistochemistry evaluation along with the treatment data was collected and analyzed.

Results: Nine cases treated at our institute had a median follow up of 41 months. Four of the five neck node primaries were treated with corticosteroids. Of the four, two had complete and two partial responses locally. Remaining one patient had partial response to surgery and corticosteroids.

Three patients with CNS presentation treated with radiotherapy to a total dose of 20–40 Gy, had complete response locally. However, two patients had simultaneous neck nodes during presentation. Partial response was seen with corticosteroids alone in one and with radiation to the neck in the other patient, of which one succumbed to myocardial infarction within 3 months post treatment. Two of them received re-irradiation to the recurrent lesions with good results.

Conclusion: Due to its rarity there is no particular guidelines regarding the management of patients with RDD. We conclude that low dose radiation either in combination with surgery or corticosteroids in nodal or extranodal lesions has shown a better local control.

Keywords: RDD; Rosai–Dorfman Disease; SHML; Sinus histiocytosis; Lymphoproliferative disease; Radiotherapy; Corticosteroids

Introduction

Rosai–Dorfman Disease is a unique lymphoproliferative disease mainly affecting the lymph nodes. Rosai and Dorfman first described it in 1969. The disease is mainly seen in children and young adults with male predominance (1). Initially, it was thought to arise in and confined to lymph nodes only. The lesion is characterized by dilatation of lymph node sinus containing large histiocytes with emperipolesis (lymphohistiocytosis), hence the diagnostic term of sinus histiocytosis with massive lymphadenopathy (SHML) was first rendered (2,3).

In its classic form, the disease presents in children and adolescents with massive painless cervical lymphadenopathy, often with associated fever, mild anaemia, polyclonal hypergammaglobulinemia, and an elevated sedimentation rate (3). Extranodal Rosai–Dorfman Disease (RDD) has been reported in approximately 43% of cases, either alone or in association with lymphadenopathy. The most common extranodal sites include the skin, orbit, and upper respiratory tract (4). Involvement of the central nervous system (CNS), especially in the absence of nodal disease, is rare, histopathology and immunohistochemistry are essential for a definitive diagnosis (5). In our experience over past three years we have had two primary intracranial RDD and one neck node recurrence case. This initiated us to conduct a retrospective analysis of last five years RDD cases presented at our institute.

Materials and methods

Eleven cases diagnosed as RDD in the department of pathology between 2010 and 2015 were included in the study, out of which two of them had come only for HPE review and they did not undergo further investigations or treatment at our center. Of the remaining 9 cases, 5 patients presented with primary neck nodal enlargement, 3 with intracranial and 1 with cutaneous disease.
All patients underwent complete blood counts with renal and hepatic evaluation. Radiological evaluation such as chest X ray, ultrasound abdomen and pelvis, CT scan of primary site and MRI of Brain in CNS cases were done. Special Investigations such as bone marrow aspiration study, biopsy and IHC were elementary.

The two patients with intracranial disease had undergone surgery of the primary site and were referred to us for further treatment and one patient with cutaneous presentation had underwent local excision of the lesion and had recurrence at same site.

Clinical features

The most common presentation seen in our patients was enlarged neck nodes (7 patients out of 9), of these 5 patients had only neck lymphadenopathy with no disease elsewhere, whereas the other 2 had intracranial disease in addition to nodal disease. One patient had isolated intracranial lesion and other had cutaneous lesions over the left thigh.

Out of 5 patients, 3 of them had bilateral neck lymphadenopathy, the other 2 had unilateral neck nodes enlargement at presentation. These patients had associated pain in neck, shoulder and ear.

Patients with intracranial disease (3 patients) presented with signs of raised intracranial pressure such as headache, blurring of vision and vomiting. In addition, patients had symptoms such as slurring of speech, aphasia, seizures and paresis of limbs.
Only one patient presented with cutaneous nodular lesion over the left thigh without lymphadenopathy. This patient underwent local excision and after one-year re-excision for recurrence at same site. The lesion again relapsed after 6 months at same site with multiple subcutaneous nodules (5 in number) around the surgical scar.

**Radiological findings**

Radiological findings of chest X ray and USG abdomen was normal for the neck primaries. CT scans of the primary in the neck showed enlarged neck nodes, which were hypo or isointense. MRI scans of the brain revealed contrast enhanced hyperintense well defined lesions on T1 and T2 weighted images (Fig 1).

Two of them were investigated with FDG PET CT scan to assess the nodal involvement along with intracranial disease. PET CT showed enhancing extra axial mass lesions with metabolic activity in both the intracranial patients showing associated neck nodes in one patient at presentation.

**Pathological findings**

The microscopic features of enlarged cervical lymph nodes showed complete effacement of architecture. The dilated sinusoids had many large histiocytes accompanied by plasma cells and lymphocytes (Fig 2a). Some of the histiocytes exhibited emperipolesis (Fig 2b). Primary CNS lesions exhibited fibrosis and infiltrate of plasma cells, mature lymphocytes and scattered histiocytes. The biopsy of cutaneous RDD histopathologically revealed similar morphology as seen in CNS disease. The immunohistochemical examination revealed strongly positive CD 68 and S–100 protein (Fig 3a & b) whereas negative for CD 30 in the cytoplasm of the histiocytes.

**Results**

Patient characteristics, treatment details and outcome are given in Table No. 1. Follow up of the above patients ranged from 3–90 months.

Three out of five patients with only neck disease were treated with oral corticosteroids (Dexamethasone 4mg BD daily for 3 months). One patient was advised observation with course of broad–spectrum antibiotics, one patient defaulted treatment on evaluation was found to have progressive disease was started on steroids later.

In patients with intracranial presentation, one patient with isolated single frontal lesion had complete excision and postoperative local radiotherapy with 3DCRT technique to a dose of 20 Gy in 10 fractions over 2 weeks. Patient was asymptomatic for one year and had recurrence in bifrontal and temporal regions with no associated lymphadenopathy and was again treated with radiation to whole brain with dose of 40 Gy in 20 fractions over four weeks along with steroids and has complete response. Second patient presented with diffuse dural lesions in posterior fossa around pons, medulla, cervical spine C1–C6 along with neck lymphadenopathy. Completely responded to radiotherapy to the posterior fossa of dose 186y in 10 fractions and 25 Gy in 8 fractions to the neck on telecobalt followed by steroids. Patient had recurrence in the cervical spine and neck lymphadenopathy with no brain lesions after eight years and responded to re–
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Presentation</th>
<th>On evaluation</th>
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<tbody>
<tr>
<td>1</td>
<td>59yrsM</td>
<td></td>
<td>Bilateral neck swelling, fever</td>
<td>Multiple B/L neck nodes, Left axillary nodes, splenomegaly and bilateral inguinal nodes.</td>
<td>Neck Nodes</td>
<td>Hodgkin’s Disease</td>
<td>Observation only.</td>
<td>Complete response.</td>
<td>74 months Alive NED</td>
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<tr>
<td>2</td>
<td>18yrsM</td>
<td></td>
<td>Right side neck swelling &amp; pain, headache</td>
<td>2010-CT scan revealed enlarged bilateral multiple neck nodes 2012-Progression in size of neck nodes</td>
<td>Neck Nodes</td>
<td>Sinus histiocytosis</td>
<td>2010-Defaulted treatment.</td>
<td>Partial response</td>
<td>29 months Alive RD.</td>
</tr>
<tr>
<td>4</td>
<td>57yrsM</td>
<td></td>
<td>Seizures, Broca’s aphasia</td>
<td>2013 MRI –Lt fronto-parietal single lesion. PET CT- No nodular involvement, 2014- Recurrence, MRI showed multiple lesions in the brain B/L frontal, Lt temporal with raised choline peaks</td>
<td>Brain</td>
<td>Meningioma</td>
<td>2013- Gross decompensation + localized RT 20 Gy/10 #. 2014- Reirradiation whole brain RT 40 Gy/20 #</td>
<td>Complete response</td>
<td>17 months Alive NED.</td>
</tr>
<tr>
<td>5</td>
<td>78yrsM</td>
<td></td>
<td>Swelling Left side of neck, left shoulder pain Right sided neck swelling, fever</td>
<td>CT scan Neck revealed left side enlarged lymph nodal mass</td>
<td>Neck Nodes</td>
<td>Lymphoproliferative disorder</td>
<td>Steroids</td>
<td>Partial response</td>
<td>48 months Alive, RD.</td>
</tr>
<tr>
<td>7</td>
<td>55yrsM</td>
<td></td>
<td>Bilateral neck swelling</td>
<td>CT scan showed enlarged bilateral multiple neck nodes</td>
<td>Neck Nodes</td>
<td>RDD</td>
<td>Steroids</td>
<td>Complete response</td>
<td>12 months Alive NED.</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics and clinical findings

RDD – Rosai-Dorfman Disease, NED—No evidence of disease, Rt—Right, Lt—Left, B/L—Bilateral, LMN—Lower Motor Neuron, IMRT—Intensity Modulated Radiotherapy, MI—Myocardial Infarction, MRI—Magnetic Resonance Imaging, PET—Positron Emission Tomography, CT—Computerized Tomography, RD—Residual Disease, SD—Stable Disease, BMA—Bone Marrow Aspiration, UL—Upper Limb, LL—Lower Limb
irradiation with 39.6 Gy in 22 fractions over 4 weeks on telecobalt followed by steroids. Third patient had diffuse supra and infratentorial dural lesions with hydrocephalus. VP shunt and partial excision was done followed by radiotherapy with 39.6 Gy in 22 fractions along with steroids to the residual disease. Responded well to the treatment but succumbed to myocardial infarction after three months of follow up.

One patient with cutaneous recurrent disease of the left thigh with associated lymphadenopathy, had recurrent multiple nodules around the surgical scar after 6 months of re–excision. Completely responded to local steroid ointment and oral doxycycline 100 mg for six months.

**Discussion**

Rosai–Dorfman disease or extranodal sinus histiocytosis with massive lymphadenopathy is an uncommon but well defined histiocytic proliferative disorder and has a benign course. It has been reported worldwide and the literature is limited to the case reports with short follow up. There are no prospective/ randomized studies defined to evaluate the therapeutic approach of the disease due to its rarity. The age group presentation reported in the literature with extranodal disease especially for isolated intracranial Rosai–Dorfman Disease is greater than that of patients with the classical disease. Similarly, in our study we observed that the average age of presentation was 43 years and 47 years for the neck/cutaneous and intracranial primary disease respectively. Male predominance was higher compared to female with a ratio of 8:3.

The most frequent clinical presentation of classical systemic RDD is a massive bilateral and painless cervical lymphadenopathy with fever, night sweats and weight loss in about 90% of patients. Only two of our patients had fever and night sweats during presentation. Though the extranodal involvement including the paranasal sinuses, skin, bone, and orbit, occurs in 43% of cases, the cutaneous RDD confined to the skin without lymphadenopathy are most uncommon. The cutaneous RDD is well defined entity and is different from the systemic RDD which can present as solitary or multiple, macular or papulonodular, xanthomatous or erythematous, dermal or subcutaneous lesions. Cutaneous RDD can involve any site including face, ears, trunk, extremities or genitalia. One of our patient had papulonodular lesion in cutaneous presentation.

Evaluation of RDD is mostly challenging, as usually it is misdiagnosed without a biopsy and proper pathological evaluation. RDD in neck nodes may clinically imitate Hodgkin’s/non–Hodgkin’s lymphoma, Langerhans cell histiocytosis, granulomatous lymphadenitis, infectious processes, reactive lymphadenopathy, other histiocytes, lymphoproliferative disorders, and metastatic carcinoma. Most previously reported cases of intracranial Rosai–Dorfman disease showed dural attachment, and radiologically mimicked meningioma, germinoma or sarcoidosis. The lesions can be solitary or multiple at the time of presentation. The skin lesions have been clinically misinterpreted as other dermatological disorders such as vasculitis, acne vulgaris, lupus vulgaris, sarcoidosis, hidradenitis suppurativa, granuloma annulare, and other histiocytes. Similarly, two of our patients were diagnosed as sinus histiocytosis and one with lymphoproliferative disorder.

On radiologic evaluation of the intracranial disease with CT scan the lesions can be seen as homogeneous hyperdense mass with prominent contrast enhancement and possibly associated with mass effect on adjacent structures due to perilesional vasogenic oedema or bone erosions. The findings on MRI usually reveals well–defined isointense single or multiple lesions in brain parenchyma on T1–weighted images and on T2–weighted images RDD lesions appear to be heterogeneous hypo–or isointense masses similar to that of the contiguous dura. These lesions are homogenously enhanced on administration of contrast with gadolinium. The role of FDG PET CT scan is not yet established and there are very few reports about it. Two of our patients with intracranial disease were initially reported as meningioma in view of dural proximity/involvement. But, subsequently diagnosed as RDD on post–operative histopathological and immunohistochemistry evaluation.

Most patients with Rosai–Dorfman disease follow a good clinical course and regress spontaneously, hence observation is also acceptable in its management. The mortality of patients with intracranial Rosai–Dorfman disease is approximately 7% (13). The pathophysiological findings suggest that Rosai–Dorfman disease is an expression of immune system dysfunction or possibly even an autoimmune process, indicating that corticosteroid treatment could be appropriate. The understanding of the choice of treatment is limited as RDD is a rare disease. Hence, the management has to be tailored according to the disease presentation.

Surgery has been the mainstay of the treatment in operable nodal and extranodal sites and when the mass is surgically resected, the patients usually improve postoperatively. Most of our patients underwent surgery whenever it was feasible. Many chemotherapy agents are used in history such as anthracyclines, vinca alkaloids, methotrexate/6–mercaptopurine, either as single agents or in combination with limited response. Hence chemotherapy was not tried in our patients. Among all the
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Adjuvant treatments available, low dose radiotherapy has shown the better results (14). There was very good response to low dose radiation up to 20 Gy planned in two of our patients with limited portals for localised/completely resected lesions and the diffuse/multiple lesions planned with large fields were treated for a biologically equivalent dose of 40 Gy with conventional fractionation.

However, relapse of Rosai–Dorfman disease has been encountered in some cases, despite surgical treatment to overcome these, patients have received corticosteroids, anticancer agents, or radiotherapy (9,10,11,12). In our study, two of nine patients who received re-irradiation for recurrence showed complete response. Those having steroid resistant tumors and who refused surgery have responded well to radiotherapy according to the published reports in primary sites such as intracranial, skin, pituitary and orbit (23,24,25,26).

Summary

Although the most common site of involvement of RDD is neck nodes, the extranodal site involvement is well documented. Histologically the presence of histiocytes exhibiting emperipolesis and strong positive to S 100 and CD 68 are the key features for the diagnosis. RDD is a self-limiting disease and surgery is considered as the main modality. However, low dose radiation in combination with surgery and/or corticosteroids for nodal and extranodal RDD has shown a better local control. Likewise, recurrent tumors were well-controlled with re-irradiation and corticosteroids.

Acknowledgements

We thank Dr. Rekha V Kumar, Head, Department of Pathology for giving us permission to retrieve the patients’ data from the departmental records. We also acknowledge all the colleagues directly or indirectly involved in this study.

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