

Case Study

EXTRANODAL ROSAI – DORFMAN DISEASE OF OROPHARYNX: A RARE DISEASE WITH UNUSUAL SITE OF PRESENTATION

ABSTRACT:

Rosai – Dorfman disease is a rare histiocytic disease which is most frequently seen in children and young adults. Extra nodal site of oropharynx is rare. A rare case of extranodal Rosai-Dorfman of oropharynx is described here involving a 54 year old female who presented with difficulty in swallowing. Patient underwent incisional biopsy from the growth vallecula and the diagnosis of Rosai – Dorfman disease was made. Patient was initiated on mercaptopurine and prednisolone as the general condition of the patient was not permeable to undergo any surgical procedure and radiation therapy. Unfortunately the patient had progressive dysphagia and expired in between the treatment.

KEY WORDS:

Rosai- Dorfman disease, dysphagia, mercaptopurine, radiation therapy, chemotherapy, surgery.

INTRODUCTION:

Rosai- dorfman disease is a histiocytic disorder which is also known as sinus histiocytosis with massive lymphadenopathy.¹ Its etiology is unknown, because of its non malignant nature treatment is indicated in only in symptomatic patients and also in patients with involvement of vital organs or system.² Surgery is the treatment modality of choice in symptomatic patients with limited /localized disease. Radiation therapy is indicated in patients with post surgical symptomatic residual disease.²

CASE REPORT:

A 54 year old lady presented with complaints of difficulty in swallowing since 1 year which was gradually progressive in nature. Patient also had history of fever which was on and off in nature and not associated with chills and rigors. There was also history of pain abdomen for two months

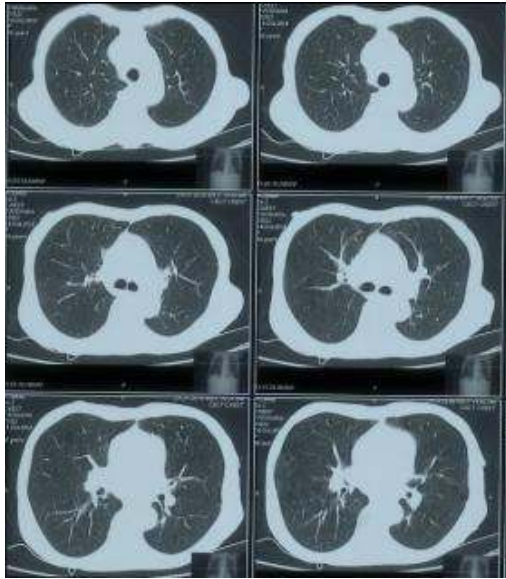
which was colicky in nature intermittent, no variation in the intensity of pain with food intake. Patient also gave the history of decreased appetite and weight loss. There was no history of difficulty in breathing, hoarseness of voice. Her past history, medical history, family history and obstetrics history was insignificant. On general physical examination patient was poorly built and nourished. On local examination of oral cavity aphthous ulcers present over the dorsum of the tongue, remaining part of the oral cavity was normal on inspection and palpation. On palpation of the oropharynx there was induration felt at the base of the tongue. On indirect laryngoscope examination ulcerative growth was seen at the base of the tongue which was extending or involving the vallecular region. There was no any cervical lymphadenopathy on inspection and palpation. Systemic examination of the patient was normal. Patient was non reactive for HIV, HBsAg (Hepatitis B surface antigen) and Anti HCV antibodies by ELISA method. Complete blood hemogram examination showed the following results: hemoglobin- 9.2 gm/dL, total leucocyte count – 7000 cells/ mm³, platelet count-3.0 lakhs/ mm³, on peripheral blood film-dimorphic picture was seen. Renal function tests which included blood urea – 24mg/dL, serum creatinine- 0.6mg/dL. Liver function results SGOT – 17 U/L, SGPT- 15 U/L. Ultrasonography of the abdomen and pelvis showed a cyst of size 1.5cm X 1.5cm in the lower pole of right kidney, gall bladder was contracted, and left kidney, liver, spleen and pancreas was normal. On barium swallow examination there was no irregularities in the esophagus (no mucosal defect or irregularity) whereas there was ill defined irregular filling defect was seen at the base of the tongue (Fig. 1). CECT scan of chest revealed no abnormalities (Fig.2) whereas CECT scan of neck revealed supraglottic and glottis edema without any obvious mass lesion seen in supraglottic and glottis area (Fig.3). Biopsy from the growth in the vallecular region showed stratified squamous mucosa with subepithelial and deeper soft tissue replaced by collection of mononucleated and multinucleated cells separated by lymphoid cells. On hematoxylin and eosin staining there was proliferation of histiocytes with large vesicular nucleus and abundant light eosinophilic cytoplasm, some of which have intact lymphocytes within their cytoplasm (H&E 200x, 400x) (Fig 4a & 4b). On immunohistochemical analysis histiocytes are strongly positive for S-100 protein (IHC 100x) (Fig. 5) and cytokeratin positive in overlying epithelium and glands and negative in histiocytes (IHC 40x) (Fig. 6).

Based on histopathological proof and immunohistochemistry profile diagnosis of Rosai-Dorfman disease was made. Due to the poor general condition and in view of the high post

operative surgical morbidity, surgery and radiotherapy was not planned. So ultimately patient was planned for Prednisolone and Mercaptopurine based chemotherapy as a salvage treatment modality. Dose schedule of chemotherapy regimen as follows tablet Mercaptopurine 50mg from D1- D30 per orally every day and tablet Prednisolone 20 mg from D1-D5 per orally every day. Unfortunately the patient had progressive dysphagia and expired in between the treatment.

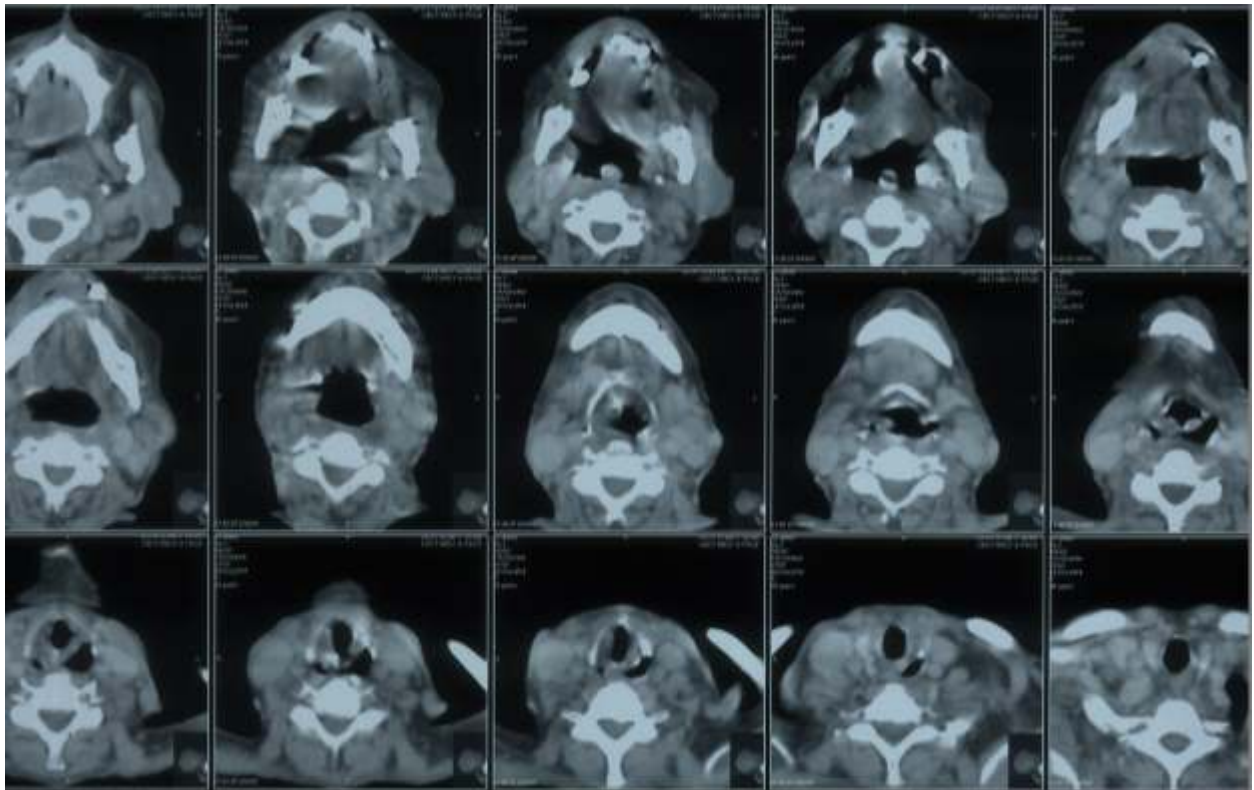


Fig. 1: On barium swallow examination there was no irregularities in the esophagus (no mucosal defect or irregularity) whereas there was ill defined irregular filling defect was seen at the base of the tongue.



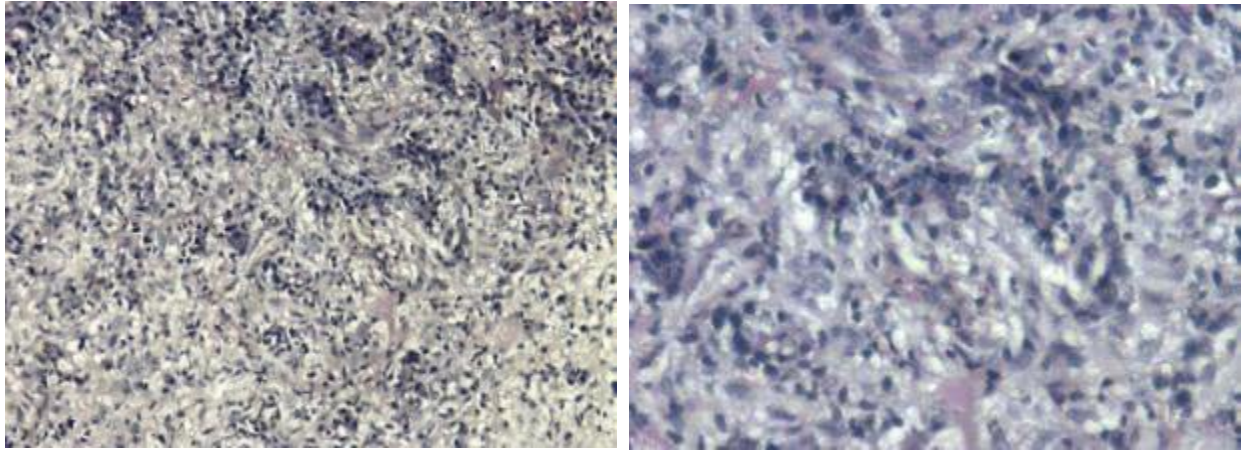
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68 Fig. 2: CECT scan of chest revealed no abnormalities.



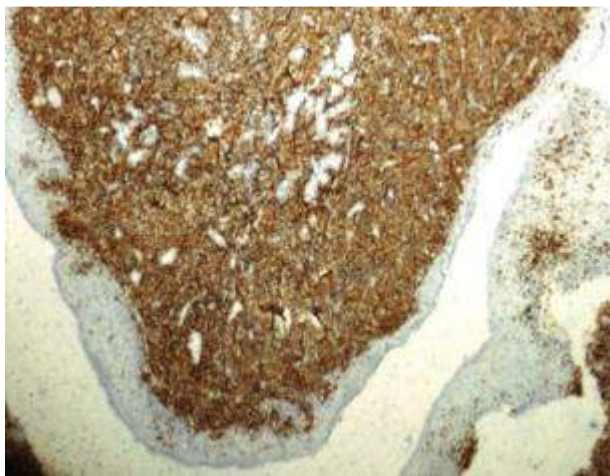
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70 Fig. 3: CECT scan of neck revealed supraglottic and glottis edema without any obvious mass
71 lesion seen in supraglottic and glottis area.



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73 Fig. 4a & 4b: Photomicrograph showing proliferation of histiocytes with large vesicular nucleus
 74 and abundant light eosinophilic cytoplasm, some of which have intact lymphocytes within their
 75 cytoplasm (H&E 200x, 400x)



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77 Fig. 5: Photomicrograph showing histiocytes are strongly positive for S-100 protein (IHC 100x)



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Fig. 6: Photomicrograph showing cytokeratin positive in overlying epithelium and glands and negative in histiocytes (IHC 40x)

DISCUSSION:

Rosai – Dorfman disease is a rare histiocytic disorder which is also known as sinus histiocytosis with massive lymphadenopathy. Eventhough it was characterized as a distinct clinicopathological disorder by Rosai and Dorfman in 1969,³ originally it was described by Destombes in 1965.¹ Typically the patients with Rosai-Dorfman disease presents with fever which was also present in the patient mentioned in this case, other presentation types are leukocytosis and non painful cervical lymphadenopathy. Eventhough the lymph nodes in the neck region are most commonly involved other extranodal sites which include the skin, soft tissue, central nervous system and less commonly the gastrointestinal system.²

Incidence of extranodal diseases is 25% to 43% of patients, extranodal in some cases may be associated with lymphadenopathy.⁴ Other extra nodal sites reported in the literature are urogenital tract, breast, gastrointestinal tract, liver, pancreas and lungs. Extranodal sites in head and neck most commonly includes the nasal cavity and parotid gland⁵ in this case the extranodal site is vallecula. The various most common extranodal sites according to ascending order of incidence are skin, nasal cavity, paranasal sinuses, eyelid, orbit, bone, salivary gland and central nervous system.⁶

Rosai- Dorfman disease is most commonly seen in children and young adults, majority of cases are seen in the second and third decades of life ⁵ eventhough it is seen in all age groups it is less in older age group similar to this case.⁵ Disease is more common in male sex and also patients from African descents, in this case the patient was a female and she is a non African descent.⁷ In Rosai- Dorfman disease the nonmalignant histiocytes infiltrates the lymphnodes and also the extranodal tissue. The hall mark of the disease required for the diagnosis is Rosai-Dorfman disease (RDD) cells which exhibits emperipolesis, the non destructive phagocytosis of lymphocytes or erythrocytes.^{3,8}

1. Workup of patients with suspected RDD includes detailed history and physical examination, various investigations such as computed tomography scans of neck, chest, abdomen and pelvis for staging and metastatic workup. There is no clear cut indication

for bone marrow biopsy in all patients. Screening for Epstein Barr virus, cytomegalovirus, Human Herpes Virus – 6 (HHV 6), Human Herpes Virus-8 (HHV 8), and Human Immunodeficiency Virus (HIV) are the various laboratory investigations. Other various investigations includes rheumatoid factor, an antinuclear antibody test (ANCA), immunoglobulins levels, erythrocyte sedimentation rate (ESR). Fine needle aspiration cytology is also a useful and reliable stool for diagnosis and it can be used as alternative to biopsy in a selective patients and sites where biopsy is contraindicated.⁹ Excisional biopsy of the diseased area and immunohistochemical analysis are required for the adequate diagnosis², this investigations are essential for the diagnosis of the Rosai-Dorfmann disease.¹⁰ Immunohistochemical stains of RDD cells are positive for S-100, CD-68 and CD-163, α 1-antichymotrypsin, α 1-antitrypsin, fascin and HAM-56.⁵

Differential diagnosis of Rosai –Dorfman disease includes tuberculosis, Wegner granulomatosis, sarcoidosis, Ig G4 related disease, juvenile xanthogranuloma, Erdheim- Chester disease, Gaucher disease, Langerhans cell histiocytosis, Hodgkins lymphoma, Non Hodgkins lymphoma, Melanoma, Leukemia and Langerhans cell sarcoma.²

Rosai – Dorfmann disease is having unpredictable clinical course, there will be episodes of exacerbations and remissions which may last for many years but unfortunately 5 - 11% of patients may die which is also unfortunately seen in this case where the patient responded in well manner to the treatment initiated but the patient had progressive disease in the form of dysphagia.⁷ Because of the self limiting course and rarity of the disease there are no well defined protocols in the management of disease.¹¹ Treatment in Rosai – Dorfman disease is based on whether it is a localized or systemic/ extensive disease and also whether the patient is symptomatic or asymptomatic. In localized disease if the patient is asymptomatic the treatment options includes watch and wait policy and complete surgical resection whereas in symptomatic localized disease the initial treatment includes complete surgical resection. In patients with post operative residual disease further treatment is based on whether the patient is symptomatic or not, in symptomatic patients the radiation therapy is indicated and in asymptomatic patients wait and watch philosophy is used. If there is progression of disease after radiation therapy then various chemotherapy drugs can be used such as Steroids, Rituximab, Interferon, Retinoids,

Imatinib, Vinca alkaloids, Anthracyclines, Alkylating agents, Methotrexate, Cladribine and Clofarabine. In systemic /extensive disease, if the patient is asymptomatic the treatment options include watch and wait versus surgical resection. In symptomatic extensive/ systemic disease the initial treatment of choice includes chemotherapy which consists of Steroids, Rituximab, Interferon, Retinoids, Imatinib, Vinca alkaloids, Anthracyclines, Alkylating agents, Methotrexate, Cladribine and Clofarabine.²

Radiation therapy is used as a palliative treatment modality, there is no standard radiation dose but usually dose protocols of lymphoma are used. Doses in the range of 30Gy and 50Gy have been applied.¹² Due to the rarity of the disease and no fixed radiation doses, there is no clear cut relationship between radiation dose and the response relationship.¹³

Komp et al. reviewed 418 cases of RDD, in which radiotherapy treatment was documented in 34 patients, but the radiation dose was reported in only 18. Dose in 5 patients were in the range of 30Gy and 49Gy (complete response was seen in one patient) whereas in two patients a dose > 50Gy (one patient had partial response) was used and in eleven patients dose was less than 30Gy (partial response is seen in three patients).¹⁴

Maklad et al. used radiation dose of 30Gy in 15 fractions using 6MV LINAC photon to the mass present over the left eyelid but the disease was reappeared after 3 months of radiation therapy after the reappearance of disease the patient was treated with Rituximab, cyclophosphamide, vincristine, and prednisolone (RCVP) based chemotherapy 8 cycles with partial response, and he was reirradiated to left eyelid mass with 6 MeV electron 10 Gy in 10 fractions with complete response.¹³

Maia et al. used radiotherapy as sole treatment modality in one patient who had skin lesions with no response to steroid as first line of treatment in his case series of 8 patients, use of radiotherapy achieved a good locoregional control and patient was recurrent free during 7th year follow up but there is no details regarding the dose and technique used.¹⁵

Median survival in Rosai- Dorfman disease is 5 years, prognosis is good until it involves the vital organs.¹⁶ Maia et al. presented a series of 8 cases who presented with lymph node and/or cutaneous lesion involvement. These patients had a favorable prognosis irrespective of the treatment modality in a follow up period ranging from 15 - 80 months.¹⁵

Based on the results of Jabali et al. where they used combination chemotherapy in which they used regimen containing prednisone, 6-mercaptopurine, methotrexate, and vinblastine in which the patient showed no evidence of recurrence after a follow up period of 5.5 years¹⁷ and also based on the experience of Horneff et al. where they tried the combination of low dose methotrxate and 6 - mercaptopurine therapy for 4 months and maintenance therapy with 6-mercaptopurine for a total duration of 2 years followed by which the patient remained free of disease for a duration of 7 years,¹⁸ and also based on the results of Maia et al. who conducted a retrospective study of series of eight patients of Rosai- Dorfmann disease from the period of January 2000 and October 2012 in Hematology Service, Instituto Nacional de Ca^ncer, Brazil,in which steroids was first treatment in seven patients in whom two patients had complete response, four patients had partial response and whereas two patients had no response to the steroid treatment based on this studies we planned to initiate the treatment with 6- mercaptopurine and steroids. One of the major toxicities of methotrexate is mucositis and as our patient was having dysphagia which may further worsen if methotrexate was initiated so based upon the disadvantage associated with methotrexate, this patient was planned with chemotherapy combination consisting of 6- mercaptopurine and steroids.

CONCLUSION:

Rosai – Dorfman disease is a rare benign histiocytic disorder. Biopsy and immunohistochemical profile helps in the diagnosis and ruling out various differential diagnoses. Various common differential diagnoses such as tuberculosis, lymphomas and leukemias should be kept in mind while making the diagnosis of Rosai - Dorfman disease. In asymptomatic localized or systemic disease patients the various treatment modalities includes wait and watch phenomenon or surgery. In symptomatic patients the main treatment modality is surgery. Chemotherapy and radiation therapy are used in the palliative setting with variable results.

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