Rosai Dorfman disease - a rare cause of cervical lymphadenopathy.

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Abstract

Rosai Dorfman disease is a rare cause of sinus histiocytosis with massive lymphadenopathy, in developing countries it mimics tuberculosis and malignancies like lymphoma and its often mismanaged. A high index of suspicion is necessary for its diagnosis. It resolves spontaneously therefore observation is currently the advocated approach for its management.

Introduction

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, It is a benign disease of histiocytic proliferation with no known etiology, it is thought to be due to immune dysregulation or infection like HHV-6, HHV-8, parvovirus B19, EBV, CMV, VZV, brucella, and klebsiella; however, there the evidence in inconclusive [(1). (2)]

It presents with painless massive cervical lymphadenopathy [nodal] with fevers, But It can also involves other sites [extra- nodal] like brain, eyes, upper respiratory tract and skin[(3).] The peak incidence is in the second or third decade, and predominant in males.

Common abnormalities in laboratory tests are increased erythrocyte sedimentation rate (ESR), leukocytosis with neutrophilia, normocytic anemia, and hypergammaglobulinemia. Histopathological examination remains the mainstay of diagnosis – lymph nodes have massive sinusoidal dilation, containing histiocytes positive for S-100 and CD68, and negative for CD1a.

Rosai-Dorfman disease is seldom life-threatening disease which commonly does not require therapy. There are no defined therapeutic algorithms for its treatment. Due to the fact that in many cases spontaneous regression is observed, usually the "watch and wait" approach is used. Surgery and systemic (e.g. steroids or chemotherapy) treatment is rarely required.[(4)]

Case Presentation

We report a case of a 1 year and 10 months old girl, who is the 5^{th} child born to non- consanguineous parents. She presented with fever and anterior neck swelling for 3 months. Fevers were high grade in nature, non-specific periodicity and relieved by paracetamol. The neck swelling initially started on the right side, gradually increased to involve the whole neck. This was associated with difficulty in swallowing solid foods. She had lost 2 kg over the course of illness. There was no history of difficulty in breathing or chest pains, or night sweats. No history of vomiting, abdominal distensions, painful micturition, headache or convulsions and no TB contact. She had attained normal developmental milestones and had received all immunization according to our national schedule. This was her first admission to the hospital.

On examination she was alert, febrile with temperature spiking from 38 – 39 degrees, some palmar pallor, not jaundiced, not cyanosed, multiple smooth surfaced preauricular, submandibular, anterior and posterior cervical and supraclavicular lymphadenopathy which was firm and matted. [*Figure 1*] and no hepatosplenomegaly. Other systemic findings were normal. By this time we doubted the diagnosis of Tb adenitis, since she had persistent symptoms despite of completely more than 1 month of Anti Tb treatment.

In the ward a thorough septic work and re- evaluation of TB diagnosis was done. We did a Full blood picture which showed WBC (leukocytosis) 34.8, Neutrophil 36.2 (93.5%), Lymphocytes 0.766 (2.2%), Hb 8.65 MCV 73 MCH 22 Platelets 654 (thrombocytosis). Peripheral smear showed anis poikilocytosis, No blast cells.

She had raised CRP 296, ESR 245, ADA 218 and LDH 295 levels. We also tested for HIV test [bio line] which was Negative and Gastric aspirate for Gene Expert – Negative

Viral screening for EBV IgM and IgG, CMV IgM and IgG, Herpes I and II IgM and IgG was done to know if there was any viral etiology for the lymphadenopathy. All tests were negative.

We performed 2 Blood cultures one week apart which showed no growth. Similar urine culture also showed no growth. Cerebrospinal fluid analysis had normal protein and glucose levels and culture was normal.

CT scan Head and neck revealed multiple matted supraclavicular, cervical, submandibular and sublingual lymph nodes.

We further did an Abdominal Ultrasound which also revealed multiple para aortic lymph nodes.

At this point we thought, this could be lymphoma. Flow cytometry showed no leukemic infiltration

And fine needle aspiration [FNAC] was done from the left anterior cervical lymph node which was reviewed by a team of haemato-pathologist.

While waiting for FNAC results, she was treated with 3rd generation cephalosporin (ceftriaxone) or one week, the fevers were controlled with antipyretics (paracetamol) when required.

At this point the fevers and the swelling still persisted, her CRP And ESR continued to raise and there was persistent leukocytosis, neutrophilia and thrombocytosis in her CBC.

After 2 weeks the results of the FNAC revealed partial effacement of lymph nodes architecture by marked expansion of Sinuses by Large Histiocytic cells. Reminiscent granulomatous process and no necrosis. Immunohistochemistry was strong for **CD 68 AND S-100 POSITIVITY.**CD 1 a – Negative (R/o Langerhans histiocytosis). ZN STAIN was negative.

A diagnosis of ROSAI DORFMANN disease was made.

Anti TB medication and all other antibiotics were stopped. She started Tabs Prednisolone 10 mg twice daily for 4 weeks and then tapered off.

She was followed up for one month, the fevers subsided and the swelling reduced and started feeding well. Currently she is followed up every 3 months to assess the possibility of relapse for at least 2 years She was discharged with proton pump inhibitor (pantoprazole) and Calcium D [calcium Sandoz] supplements once daily to prevent the side effects of prolonged steroid exposure which was gastritis and osteoporosis respectively. The mother was advised to check the baby's body weight every week and test for random blood glucose at least three times in a week at a nearby health center.

Discussion

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, a rare disease with a variable presentation and course. Specific incidence and prevalence is not known for this disease with only about 1000 reported cases worldwide.[(5)] It is common in males than in females 4:1 and it affects all age groups but more frequently reported in young children and adolescents especially in the first two or three decades. Its pathogenesis remains unknown, though there is no clear causative agent in most

cases, a link between human herpes virus 6 (HHV-6), Epstein-Barr virus (EBV) and parvovirus B19 has been suggested, though not conclusive [(4)]

The clinical presentation of RDD has several predictable signs and symptoms, the most common nodal site being painless bilateral cervical lymphadenopathy reported in nearly 90% of cases.[(1),(4)]

Extra- nodal involvement is observed in approximately 40% of cases and can occur anywhere in the body with the most common sites including the skin, gastrointestinal tract, eyes, external and internal ear, skeletal system, upper and lower respiratory tracts, oral cavity, nasal and paranasal cavities, and the central nervous system[(1),(3),(6),(7)] CNS involvement is rare, and the constitutional symptoms are absent, this poses a therapeutic challenge as spontaneous remission is rare and there is no standard therapeutic protocol for its treatment. From a case series of 6 patients with CNS involvement all underwent surgical excision, followed by chemotherapy and steroids. [(7)]

Our case was a young female who presented fevers and multiple cervical, sublingual, submandibular and supra clavicular lymphadenopathy, with leukocytosis, neutrophilia, anemia, thrombocytosis, an elevated C- RP and ESR. However, the possibility of Rosai-Dorfman disease was not considered clinically till FNAC cytology reports were available. In our setting this presentation can easily be misdiagnosed as it mimics common infections like TB adenitis and malignancy like lymphoma. The differentials include reactive lymphadenitis, tuberculosis, lymphoma, metastatic carcinoma, hemophagocytic syndrome, and Gaucher's disease. Our patient was initially diagnosed as TB adenitis and kept on Anti TB medication for 1 month without any resolution of symptom's . Due to its rare occurrence this poses a diagnostic challenge. We screened her for viral etiology like EBV, CMV and herpes virus which have been linked to the etiology of this disease, the results were negative.

Our patient was diagnosed using FNAC, When compared to surgical core or excisional biopsy, FNAC can at times be misinterpreted due to limited or non-representative sampling and, as it does not permit examination of the tissue architecture, diagnosis can be further confounded.

Despite these limitations, FNAC is still a very useful tool for the diagnosis of RDD. [(8),(9),(10)]

Histology findings include alteration of the normal lymph node architecture by massive sinusoidal dilation that contains histiocytes, lymphocytes, and plasma cells. Emperipolesis within the histiocyte cytoplasm is the classical finding in RDD. The histiocytes will be positive for immunohistochemical stains CD68 and S100 and are typically negative for CD1a.

There is no unified therapeutic protocol for the treatment of this disease, spontaneous remission is observed, therefore " wait and watch" approach is recommended. [(4)]

Our patient was treated with steroids at a dose of 10mg twice daily per day (2mg/kg) for 2 weeks and then taper off over 4 weeks. She was asymptomatic after 3 weeks of starting the treatment. Surgery remains the mainstay treatment for RDD. For symptomatic patients requiring systemic therapy steroids are first-line therapeutic option that produces responses in both nodal and extra-nodal disease; however, the reliability and durability of these responses is unpredictable, furthermore the duration of treatment is also not known. Very limited clinical trials have been done using chemotherapy and radiotherapy therefore the effectiveness of these methods is still uncertain. In cases of disseminated disease chemotherapy has been used with agents such as vinca-alkaloids, anthracyclines, and alkylating agents with varying response rates. Radiotherapy is considered a palliative method in patients with symptomatic disease. [(2)] [(4)]

RDD has been postulated to remit and relapse, however the recurrence rate is unknown. We are following up our patient every 3 monthly for at least 2 years to assess for the possibility of future relapse.

The parents of this child were losing hope in the beginning, as they could not see any difference in their child's symptoms despite of all the medication and investigations that were taken. But later once she was on steroids and after thorough counselling them, they were very co-operative and appreciated our efforts to help their child.

Conclusion

RDD is a rare disease and has a relatively benign clinical course, it often mimics other diseases and malignancies and can easily be misdiagnosed. In the developing countries like Tanzania, it can easily be misdiagnosed as Tb adenitis or malignancies like Non- Hodgkin's lymphoma. A high index of suspicion is necessary for its diagnosis. Definitive diagnosis is made by histology which show emperipolesis, sinus dilatation and histiocytic cells infiltration and immunohistochemistry reveals positive S100 and CD68 markers, and negative CD1a marker. Because the disease generally resolves spontaneously, observation is currently the advocated approach.

Abbreviations

ADA Adenine Deaminase

CBC Complete blood count

CD Cluster of Differentiation

CMV Cytomegalovirus

CNS Central Nervous System

CRP C- reactive protein

CT Scan Computed Tomography Scan

EBV Epstein Barr Virus

ESR Erythrocyte sedimentation rate

FNAC Fine needle aspiration cytology

LDH Lactic Dehydrogenase

RDD Rosai Dorfman disease

TB Tuberculosis

ZN Ziehl Nelson Stain

Declarations

Ethics approval and consent to participate

Ethical Approval was not applicable.

Consent for participation was given by the biological mother

Consent for publication

Written informed consent was obtained from the patient's legal guardian (mother) for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and material

Data sharing not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

IA and HS, EK, LL admitted the baby and were attending the baby daily in pediatric ward. U.M was following up this baby in pediatric oncology. IA prepared the manuscript. LM. AM, HM are specialists who provided their expert opinion in the management of this baby.

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Legends

Figure 1 (a), (b) Bilateral neck swelling