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Case Report

Rosai-Dorfman Disease and Concomitant Hodgkin Lymphoma and Tuberculosis Activation: A Rare Case Report

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ABSTRACT

Rosai-Dorfman disease (RDD) is a rare, benign disease with extensive lymphadenopathy. In this case, an 81-year-old gentleman with previous pulmonary tuberculosis presented painless cervical lymphadenopathy associated with generalized weakness, loss of appetite, and cough. The causes of cervical lymphadenopathy in the elderly are comprehensive; thorough history, examination, and appropriate investigations are vital in diagnosing diseases. A lymph node biopsy is recommended if blood investigations and imaging are inconclusive. He was later diagnosed with RDD associated with Hodgkin's lymphoma, and dexamethasone treatment was initiated. Concomitant diagnoses are rare but should not be disregarded. This case report is a reminder that RDD remains a differential diagnosis of cervical lymphadenopathy. Regular monitoring is required as immune dysregulation from the treatment of RDD may exacerbate quiescently treated pulmonary tuberculosis.

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Introduction

Rosai-Dorfman Disease (RDD) is an uncommon disorder first described by Destombes in 1965. Rosai and Dorfman published more data on RDD in 1972.[1] The condition presents commonly in males in the first and second decades, although any age could be affected. RDD is also known as sinus histiocytosis with massive lymphadenopathy (SHML), characterized by benign proliferation of histiocytes within lymph node sinuses and lymphatics in extranodal sites. We presented a unique case of cervical lymphadenopathy in the elderly, later diagnosed as RDD associated with Hodgkin's lymphoma below. This case report serves as a reminder that RDD remains a differential diagnosis of cervical lymphadenopathy.

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Case Report

An 81-year-old male patient with a background history of dementia, seizures, and previously treated pulmonary tuberculosis, presented to the hospital with a week of generalized body weakness and loss of appetite. He denied any fever but complained of a cough with white sputum. His pre-admission medications include levetiracetam 500 mg BD, rivastigmine 1.5 mg BD, and amlodipine 5 mg OD. On examination, he had a palpable pea-sized, painless, enlarged left submandibular lymph nodes and inguinal lymph nodes bilaterally. His abdomen was soft and non-tender, but hepatomegaly was present. Other examination findings were unremarkable.

Significant laboratory results included a raised c reactive protein of 5.0 mg/dL and raised erythrocyte sediment rate of 113 mm/h. Bicytopenia with white blood cells of 3.6 x 10^9/L and haemoglobin of 10.3 g/dL. Total protein was raised at 122 g/L. Sodium was 123 mmol/L; his urea, electrolytes, and liver function tests were unremarkable. A neck ultrasound scan showed multiple enlarged lymph nodes in bilateral submandibular, anterior and posterior cervical triangles. Computed tomography (CT) thorax, abdomen and pelvis was done and showed multiple nodes measuring 5.7 mm to 9.2 mm in right paratracheal and subcarinal regions, 7.0 mm to 28.4 mm in both axillae, abdominopelvic adenopathies noted at left paraaortic (largest measuring 2.1x1.5 cm), interaortocaval (1.4x1 cm), retrocaval (1.7x1 cm), portal (2.6x2.1 cm) (*Figure 1*), coeliac (2.7x1.9 cm) (*Figure 1*), mesenteric (3.2x1.8 cm), bilateral external iliac (largest 2.3x1.5 cm on right and 1.5x1.4 cm on left) (*Figure 2*), bilateral inguinal (largest 2.3x1.4 cm on right and 2.2x1.4 cm on left) (*Figure 3*).

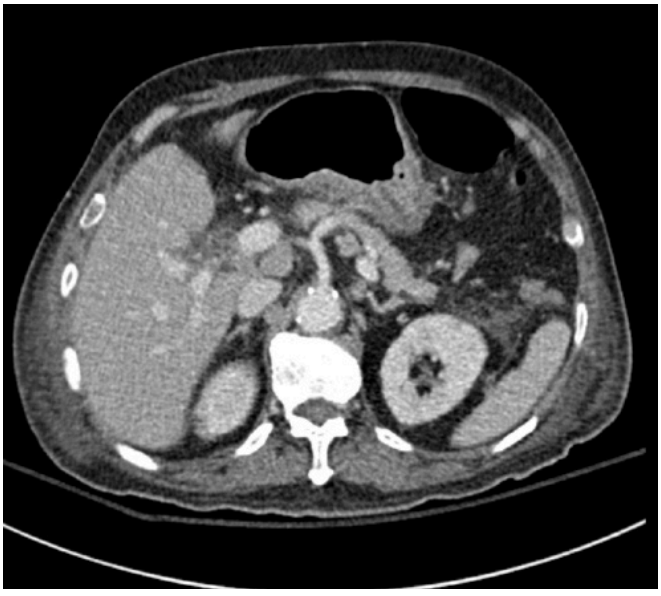

Figure 1. Radiological images

Further work-up for possible diagnoses and immunocompromised status were done, which include human immunodeficiency virus (HIV) serology, hepatitis B and C serologies, triple tuberculosis acid-fast bacteria (AFB) smear, antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) for autoimmune screening, and HbA1c for diabetes mellitus; which were all negative. His total protein was raised with anaemia, and work-up for multiple myeloma was done; lactate dehydrogenase was mildly increased at 267 U/L, but urine Bence-Jones protein and serum paraprotein at electrophoresis were both not detected. An excision biopsy of the right neck node was then performed, and the specimen was sent for a frozen section, showing dilated sinuses filled with histiocytes and lymphocytes. Histiocytes showed emperipolesis (*Figure 4*). The surrounding tissue showed a nodular arrangement with lymphocytic, plasma cell, and Reed-Sternberg (R-S) like cell infiltrate along with a few eosinophils (*Figure 5*). The histiocytes within the sinuses showed a positive reaction with S-100 (*Figure 6*), while the R-S-like cells showed a positive reaction with CD30 and CD15. The overall picture was RDD, associated with Hodgkin's lymphoma. Since Mr N was not a good candidate for chemotherapy, oral dexamethasone 4 mg BD was started with allopurinol for the risk of tumour lysis syndrome after steroid treatment.

He was re-admitted to the hospital three weeks later as his sputum cultures grew *Mycobacterium tuberculosis complex*. Two months of intensive therapy consisting of isoniazid, rifampicin, ethambutol and pyridoxine were initiated, followed by seven months of isoniazid and rifampicin. His dexamethasone dose was subsequently reduced to 2 mg BD.

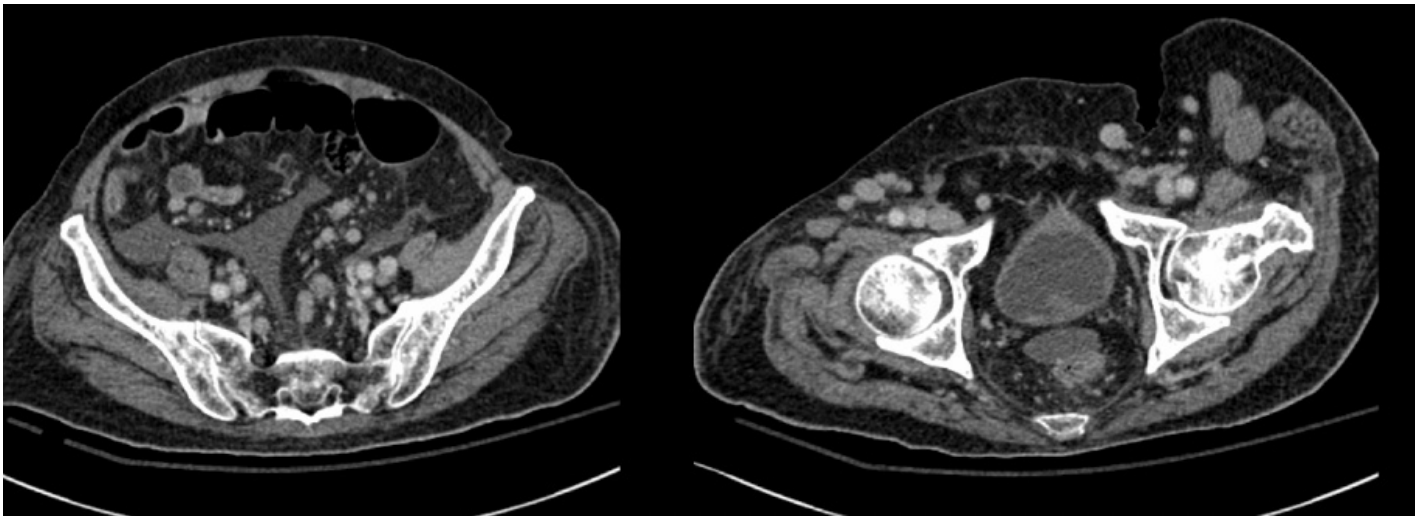

Figure 2 and 3. Radiological images

Discussion

Patients with RDD usually present with nonspecific findings such as low-grade fever, cervical lymphadenopathy, normochromic anaemia, elevated ESR, leukocytosis (mainly neutrophilia), and hyperglobulinemia.[1] These were consistent with his initial presentation, although he did not report any fever and had leukopenia. Cervical lymphadenopathy in the elderly is a common presenting complaint but could be caused by a vast array of diseases, including bacterial infections, e.g. cat scratch disease; viral infections, e.g. hepatitis B, HIV; *Mycobacterium tuberculosis*; cancers, e.g. leukaemia and lymphoma, lymphoproliferative disorders, e.g. RDD, hemophagocytic lymphohistiocytosis; autoimmune disorders, e.g. systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, or medications, e.g. atenolol, captopril, carbamazepine, lamotrigine, and phenytoin.[2] Most patients with RDD present with chronic bilateral, painless cervical lymphadenopathy. Notably, if only one lymph node group was enlarged, this was commonly the submandibular region,[1,3] similar to our case. Our case also had inguinal and axillary lymph nodes, usually less prominent than cervical involvement in RDD.

Evaluation of lymphadenopathy causes should be based on history and physical findings, followed by routine blood investigations, HIV testing, and chest X-ray. If unremarkable, further assessments such as tuberculosis, ANA, syphilis, and heterophile tests should be considered.[2,4] He had most of the research done, except for syphilis and the heterophile test. None of his drugs was found to cause lymphadenopathy. For an uncertain diagnosis, a lymph node biopsy was recommended first.

In SMHL, histological findings of lymph nodes include capsular and pericapsular fibrosis, with numerous histiocytes containing lymphocytes in their cytoplasm (emperipolesis). Emperipolesis, the presence of an intact cell within the cytoplasm of another cell, is of great diagnostic significance for RDD, despite not being pathognomonic. In the initial phase of the disease, prominent dilatation of sinuses was reported. Both emperipolesis and dilated sinuses were seen in our case too. These sinuses would later be occupied by mainly histiocytes and other cells such as lymphocytes, plasma cells and occasional neutrophils, resulting in effacement of nodal structure.[1,3,5] Histiocytes characteristically demonstrate reactivity to CD11c, CD14, CD33, CD68 antigens and S100 protein. They are usually CD1 negative. Differential diagnoses for SHML include reactive sinus histiocytosis, Langerhans cell histiocytosis, malignant histiocytosis, hemophagocytic syndrome, tuberculosis, and lymphoma. Each of the differentials has characteristics to distinguish them from SHML. For instance, reactive sinus histiocytosis expresses CD68 but lacks S100 and CD1a. On the contrary, Langerhans cells

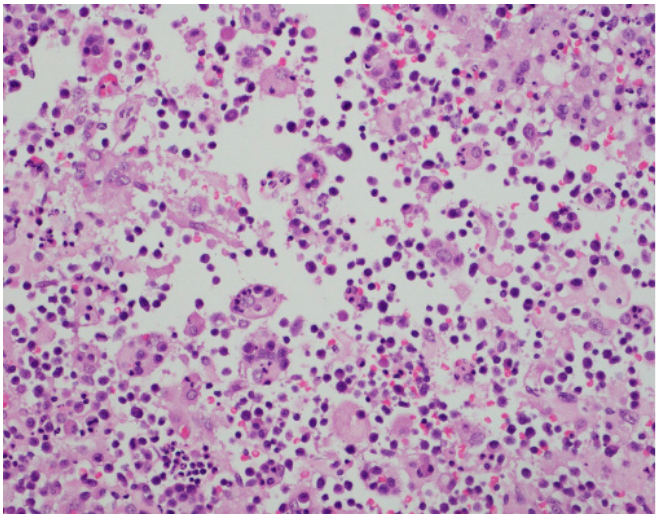

Figure 4

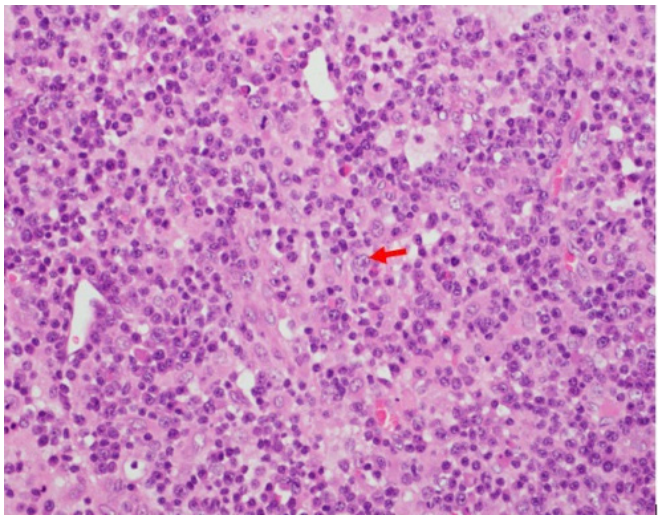

Figure 5

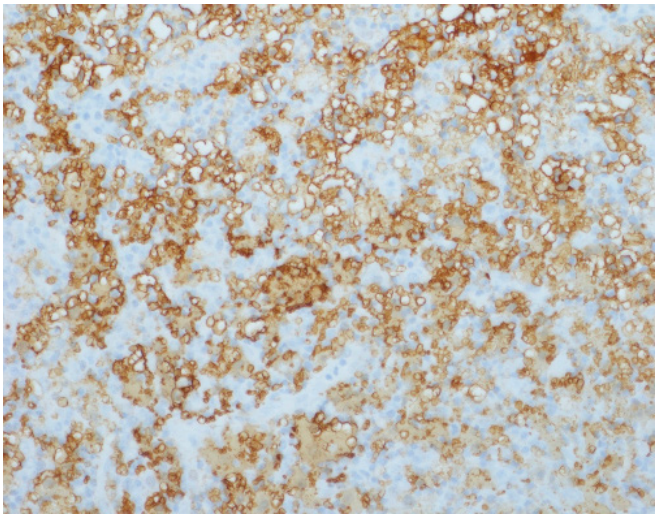

Figure 6

are reactive to S100 and CD1a. They also show Birbeck's granules on electron microscopy. Malignant histiocytosis demonstrates prominent cellular atypia and mitosis, which is rare in SHML. Hemophagocytic syndrome is associated with pancytopenia and hepatosplenomegaly, which are generally absent in SHML. SHML can be differentiated from tuberculous lymphadenitis as tuberculosis would show epithelioid cell granuloma with or without caseous necrosis. Lastly, non-Hodgkin's lymphoma consists of lymphoid cells that show positivity for CD3 (T-cell), CD20 (B-cell), or bcl-2 (anti-apoptotic) marker, while Hodgkin lymphoma contains RS cells reactive to CD15, CD30 or CD20; these are usually negative in SHML.[3,5]

His biopsy showed a positive reaction to S-100, CD30 and CD15, which concluded he has a dual pathology of RDD with Hodgkin's lymphoma and thus warranted treatment as recommended by haematology colleagues. A literature review done by Edelman et al.[6] showed 25 cases of RDD associated with Hodgkin and non-Hodgkin lymphoma, in which 70% of the dual pathologies were diagnosed simultaneously. Sporadic RDD is the most common form of RDD, which include classic nodal, extranodal, neoplastic related, and immune disease-related RDD. Classic RDD is the most prevalent type affecting children and young adults in the first two decades. Extranodal disease is more common in older patients and involves skin, nasal cavity, bone, orbital tissue, and central nervous system. As RDD can co-exist with neoplasia, pathological findings of RDD should be present in more than 10% of the tissue to establish neoplasia-associated RDD.[7]

In addition, our case was later diagnosed with tuberculosis through sputum cultures and received treatment. His tuberculosis was likely a reactivation of the disease, as he was treated for it many years back. The Hodgkin's lymphoma and dexamethasone may suppress the cell-mediated response, which facilitated the mycobacterial infection.[8,9] There has also been documented literature on tuberculosis preceding the onset of RDD with no known causative link; however, this could be attributed to the high prevalence rate in Asian countries.[10] Several reports recorded patients

presenting with symptoms mimicking tuberculosis but were later diagnosed as RDD.[11-13] A study done in Pakistan also showed that the most common causes of lymphadenopathy include tuberculosis (70.45%), followed by reactive lymphadenitis (13.63%), metastases (11.36%), lymphoma (4.54%), and chronic nonspecific lymphadenitis (2.27%).[4] There is potential for misdiagnosis as RDD, tuberculosis and Hodgkin's lymphoma as they present similar signs and symptoms such as fever, cough, loss of appetite, and adenopathy.[8] It is essential to diagnose patients to ensure they receive the proper treatment correctly.

Lymphadenopathy in RDD will eventually regress without treatment, despite waxing and waning over months to years. Therapy with corticosteroids usually shows an excellent clinical response. Other treatments include alkylating agents, vinca alkaloids, and low-dose interferon. Radiation therapy and surgical treatment can be used for life-threatening obstructions due to pressure exerted by lymph nodes. Patients generally have a good prognosis unless they have associated immunological pathologies, extranodal involvement, especially of kidney and liver, or younger age group.[3,5] Long-term follow-up is essential to monitor the course of the disease and reactivation of tuberculosis

Conclusions

RDD is usually diagnosed clinically and confirmed by laboratory investigations. Albeit rare, it should remain a differential diagnosis for cervical lymphadenopathy. Patients may present with concomitant pathologies; hence, it is crucial to do a full work-up for patients to ensure proper treatments can be delivered. Regular surveillance for tuberculosis reactivation should always be considered, especially in highly endemic countries.

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Conflict of Interests

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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