Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman Disease): report of a case in a Nigerian Teaching Hospital

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Abstract

Sinus histiocytosis with massive lymphadenopathy (SHML) is a rare, benign disease of unknown aetiology. This disease typically presents with massive, painless cervical lymphadenopathy but may occur in a wide variety of extranodal sites. This report describes a 43-year old man with a left submandibular swelling and left lateral cervical lymphadenopathy clinically suggestive of a malignancy. Initial cytological examination of a fine needle aspirate specimen taken from the mass suggested a chronic granulomatous inflammatory lesion. A definitive diagnosis of SHML was however made only after excisional biopsy of the lesion. The patient was followed up for 6 months and no recurrence of the lesion was observed.
SHML may be considered a rare lesion among Nigerians. Knowledge of its clinical presentation with understanding of the differentials diagnosis is important to avoid unnecessary intervention. The diagnosis can be made from FNAC, histopathology and immune-histochemistry. There is no ideal protocol for the treatment. Follow-up is however necessary to detect relapses.

Key words: Sinus histiocytosis; lymphadenopathy; Nigerian

Introduction

Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease, is a rare benign Histiocytic proliferative disorder of unknown aetiology[1]. It was initially described by Rosai and Dorfman in 1969[1], and was further described in greater detail in 1972[2]. It clinically presents as massive bilateral painless cervical lymphadenopathy in about 90% of cases, although other lymphnode involvements have been reported[3, 4]. Goodnight et al[3] reported extranodal involvement in about 30-40% of cases. Although the disease may occur at any age, children and young adults have been observed to be generally more affected with an average age of 19.7years[1,2,5,6]. A male-to-female ratio of 1.4:1 has been reported[3]. The aetiology of SHML is unknown but factors such as infection from Klebsiella, Epstein-Barr virus and Varicella zoster virus as well as autoimmunity have been implicated in its aetiopathogenesis[6]. The disease is often a self-limiting disease but because of its variable clinical course, treatment modalities such as surgery, radiotherapy or the use of corticosteroids, cyclophosphamide or most recently, interferon used either solely or in combination have been used in its management[7-9].
Histologically, the lymph node sinuses in SHML are typically distended by plasma cells and histiocytes that contain abundant eosinophilic cytoplasm, and round to oval vesicular nuclei[1, 2]. Despite its benign and self-limiting nature, the clinicopathological presentation of SHML may be easily misinterpreted as other malignant histiocytic proliferative disorders (such as lymphomas, Hodgkin's disease, Langerhans histiocytosis X, monocytic leukemia and metastatic carcinoma) resulting in inappropriate treatment and unnecessary complications[1-3, 5-6]. It is therefore important that the clinicopathological characteristics of SHML is well understood to prevent misdiagnosis and subsequent mismanagement.
Although SHML has been reported worldwide in the scientific literature[1-9] to the best of our knowledge, reports on clinicopathological characteristic of SHML in Nigerians is rare in the scientific literature [10,11]. We present the clinicopathological characteristics of the first case of SHML that was diagnosed and treated at the Lagos University Teaching Hospital in 40 years, with the hope that information from this report would be used to update information in the scientific literature.

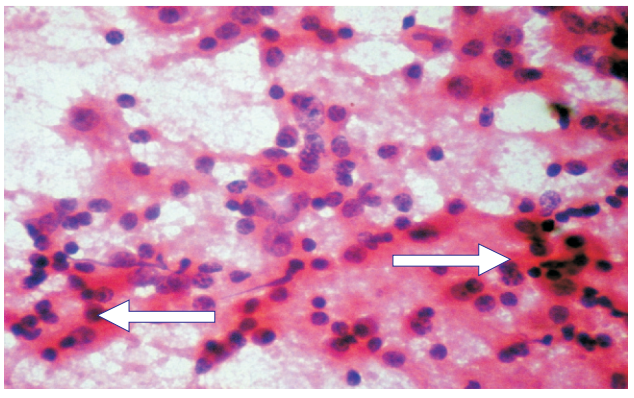

Figure 1: Photomicrograph of fine needle aspirational cytology showing presence of numerous lymphocytes and multinucleated giant cells (arrow). (Hand E stain x 400)

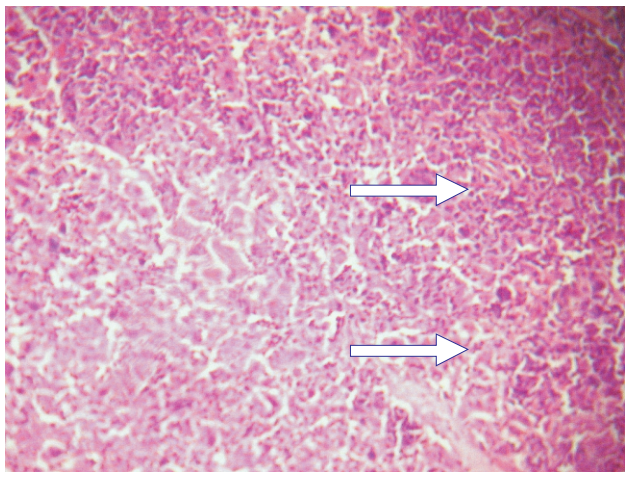

Figure 2: Photomicrograph showing aggregates and sheets of large histiocytic cells with small round to oval nuclei and foamy to lightly eosinophilic cytoplasm and some histiocytes exhibiting phagocytosed intracytoplasmic lymphocyte (arrow) (emperipolesis). (H&E X 200)

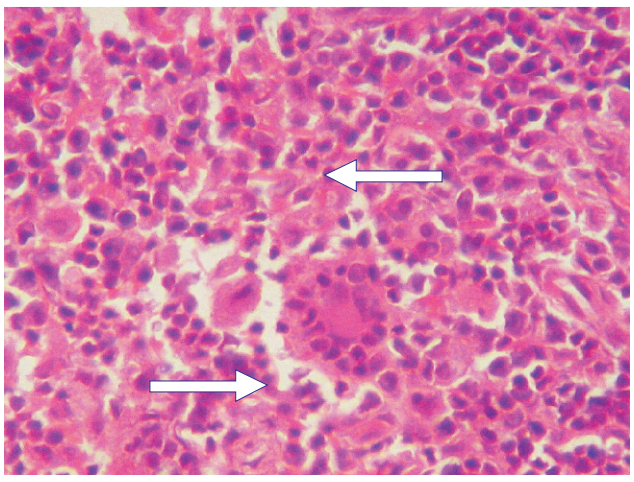

Figure 3: Large histiocytic cells with small round to oval nuclei and foamy to lightly eosinophilic cytoplasm and some histiocytes exhibiting phagocytosed intracytoplasmic lymphocyte (arrow) (emperipolesis). (H&E X 400)

Case report

A 43-year old Nigerian male presented at the out- patient clinic of the Oral & Maxillofacial Surgery Unit of the Lagos University Teaching Hospital with a left sided neck swelling of 6-months duration. He gave a history of a painful mandibular left second molar, which was extracted a month prior to the development of the swelling. In addition, the patient stated that the swelling persisted even after a course of antibiotics was administered. Extra-oral examination of the patient, revealed a rubbery left submandibular swelling of approximately 6cm x 5cm that was not attached to the overlying skin or underlying structures. In addition, there was a diffuse, slightly tender left lateral cervical swelling observed around the sternocleidomastoid muscle. Intra-oral examination however revealed the extraction socket which had healed satisfactorily. Fine needle aspiration cytology (FNAC) smears of the left submandibular and maxillary deep

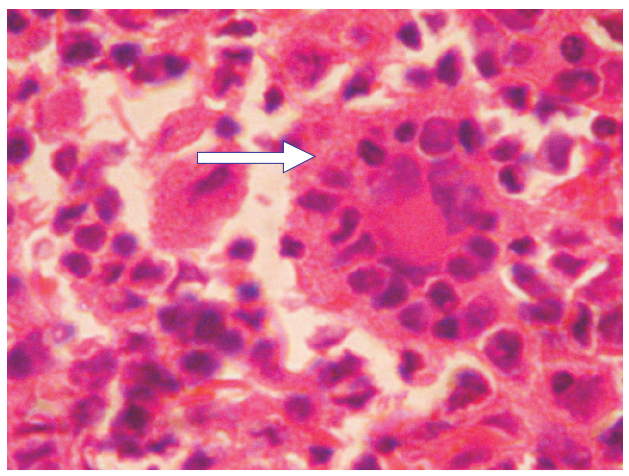

Figure 4: The lesion is remarkable for the presence of histiocytes exhibiting phagocytosed intra-cytoplasmic lymphocyte (arrow) (emperipolesis). These are arranged in wreath like rings within the eosinophilic cytoplasm of the histiocytes. (H & E, x1000).

cervical lymph nodes showed a lesion that comprised of uniformly distributed reactive lymphocytes interspersed by multinucleated giant cells, isolated macrophages and tingible body macrophages. The giant cells contained regularly outlined multiple nuclei and abundant eosinophilic cytoplasm **(Figure 1).** A diagnosis consistent with a chronic granulomatous inflammatory lesion was made.

Ultrasonography examination revealed smoothly outlined, solid, round and well marginated hypoechoic masses of varying sizes observed in the left submandibular region, suggestive of enlarged, unmated lymph nodes. The sizes of the masses measured 38mm x 36mm, 53mm x 29mm and 27mm x 18mm. A provisional diagnosis of lymphadenopathy was made. Baseline haematological values were essentially normal with white blood cell count of 3900mm3, (60% polymorphs, 35% lymphocytes, 7% eosinophils and PCV of 34%). Surgical excision of all involved lymph nodes was done under general anesthesia, and specimens were sent for histological examination.

Gross specimen of lesions showed multiple fragments of lobulated firm nodal soft tissue with a yellowish- brown cut surface. Haematoxylin and eosin stained sections of the tissue revealed multi-sected fibrotic encapsulated lymphoid tissues containing histiocytes with round to oval vesicular nuclei **(Figure 2)**. These histiocytes exhibited phagocytosed intra- cytoplasmic lymphocytes (emperipolesis) that were arranged in wreath like rings within their eosinophilic cytoplasm **(Figures 3 and 4)**. There were occasional areas of necrosis observed within the tissue. A diagnosis of sinus histiocytosis with massive lymphadenopathy was made.

The patient was discharged four days after surgery. Follow-up revealed that the patient had signs of weakness of the left arm and deviation of the mouth to the left side upon mouth opening (neuropraxia). The patient has been followed up for 6 months and so far, there has been no report of recurrence of the lesion observed in the patient. Improvement of facial nerve weakness was also observed before the patient was lost to follow-up.

Discussion

Sinus histiocytosis with massive lymphadenopathy (SHML) is a benign, self-limiting disorder that commonly involves the lymph nodes[1]. Destombes in 1965[12] initially described this lesion, and Rosai and Dorfman[2] gave a better description in 1972. Since then over 600 cases have been reported in literature and the largest review to date of 423 cases was done by Foucar et al.[13]. SHML is currently classified as one of the non-Juvenile Xanthogranulomas (non-JXG) under the sub-group of the non-Langerhans Cell Histiocytosis (non-LCH)[14]. Although aetiology of SHML is still unclear, suggestions of it being a reactive process or an infection rather than a neoplasm (molecular studies conducted have found no evidence of clonal re-arrangement) have been made[15-17]. It has been inferred that undefined immunological defects initiated by certain organisms such as Epstein Barr virus[13, 18, 19], Human herpes virus[18] and Cytomegalovirus[20] may play a role in the aetiopathogenesis of the disease. A genetic predisposition in some patients with this condition has also been implied because of reports of familial cases with the disease in seven pairs of siblings including three sets of identical twins[21]. Most cases of SHML occur during the first or second decade of life with a mean age of 19.7 years[6]. Males are reported to be more affected than females with a male-to-female ratio of 1.4:1 to 2:1[3,22].

The disease has been reported worldwide and American blacks, and the Caribbeans are more frequently affected (43.6%)[1]. The affected patient may present with enlargement of cervical, inguinal, axillary and mediastinal lymph nodes but classically, in approximately 90% of cases, patients present with bilateral cervical lymphadenopathy[1,13]. Other symptoms include pain (although some may be painless), fever, haematologic/immunologic abnormalities such as anaemia (usually mild normochromic microcytic or hypochromic microcytic), positivity for red blood cell autoantibodies, an elevated erythrocyte sedimentation rate (90% of cases), or a polyclonal hypergammaglobulinaemia (in 90% of cases)[5, 13]. Affected patients are rarely positive for rheumatoid factor, anti-nuclear autoantibodies, or systemic lupus erythematosus[5, 13]. One study demonstrated a reversal of the CD4: CD8 ratio of circulating lymphocytes[13].

Technically the name Rosai-Dorfman Disease (RDD) applies to cases with extra-nodal disease without concurrent lymph node involvement; however, it is often used in cases that have extra-nodal involvement regardless of the lymph node status[13]. In the review of 423 patients by Foucar et al[13], 43% of cases had at least one site of extra-nodal involvement as well as lymph node involvement, while 23% of cases had extra-nodal involvement only. The most frequent extranodal sites in decreasing order are skin, nasal cavity and paranasal sinuses, soft tissue, eyelid and orbit, and bone. The head and neck were involved in 22% of extranodal disease[5,6,13] and the common sites involved are nasal cavity, paranasal sinuses, nasopharynx, submandibular and parotid glands, the larynx, temporal bone, infratemporal fossa, pterygoid fossa, the meninges and the orbit[5,6,13,23]. Imaging (CT and magnetic resonance imaging) may be used to assess the extent of the lesion[23].

The present case presented with multiple cervical and submandibular lymphadenopathy, with a normal haematological picture. However, the possibility of Rosai-Dorfman disease was not considered until histologically determined. Studies have shown FNAC to be a reliable aid to the diagnosis of the lesion[24-26]. Cytology smears usually reveal numerous large histiocytes with abundant pale cytoplasm and phagocytosed lymphocytes (emperipolesis) which was observed in the FNAC of the patient in this report. Gross examination of lymph nodes affected with SHML shows either a nodular or diffuse yellow-white cut surface with capsular or pericapsular fibrosis. Microscopically the sinuses are typically distended by plasma cells and histiocytes containing abundant eosinophilic cytoplasm, and round to oval vesicular nuclei, usually containing one small nucleolus[13, 27]. One of the characteristic histological features is the presence of emperipolesis. Emperipolesis, unlike phagocytosis have lymphocytes that are intact and not attacked by enzymes. Less commonly plasma cells, red blood cells and neutrophils may be seen within the histiocytes. However the SHML histiocytes do not demonstrate cytologic atypia characteristic of neoplasms[13, 27]. The lymph node capsule may be fibrotic, and infiltrated with lymphocytes and plasma cells. In extranodal cases, the emperipolesis is less evident[13, 27].

In the present case, FNAC and cervical biopsy were performed to exclude the possibility of neck metastases from local malignancies. In addition, ultrasonography of the neck demonstrated the extent of the disease. Differential diagnosis consists mainly of histiocytic proliferative disorders that present with distention of the sinuses. These include lymphomas, Hodgkin's disease, Langerhans cell histiocytosis X (LCH) and monocytic leukemia and metastatic carcinoma[27]. LCH tends to have a smaller nucleus than SHML and a characteristic groove. Eosinophils are not a noticeable feature of SHML unlike LCH. In addition, LCH is S-100 positive but unlike SHML, CD1a positive. Sinus hyperplasia, another differential shows less distended sinuses and has S-100 negative cells[27].

The clinical picture and capsular fibrosis may suggest Hodgkin's lymphoma but CD15 negative Reed Sternberg cell are not seen in cases of SHML[28]. SHML is negative for keratin thus excluding diagnosis of metastatic carcinoma, although, positivity of SHML for S-100 may suggest metastatic melanoma[28], However melanoma stains positively for HMB45 and MelanA in addition to S-100[27,28].

Currently, there is no established ideal treatment for SHML. The disease in most cases undergoes spontaneous remission. In a review of 80 cases by Pulsoni et al, 80%of patients had full remission[6]. Treatment may be necessary in cases of enlarged tissue with significant symptoms such as compression on vital organs or airway obstruction [29]. Surgeons have recommended surgery as the first line of treatment with steroids, chemotherapy or radiation used as adjuncts[9]. Cases of extranodal or extensive involvement of tissues usually require multiple treatment modalities and radiotherapy[30]. Chemotherapy with methotrexate and 6-mercaptopurine[16, 29], alpha interferon[6] have all been used with variable results obtained.

It is worth noting that the prognosis of SHML is good. However, cases of aggressive and widespread dissemination, involving organs like the kidneys, lower

respiratory tract, or liver or presenting with immunologic abnormalities or anaemia are often of worse prognosis[13,19] and may cause death[6]. Recurrence in such cases is often high even after successful treatment[1]. The present case was treated with surgery to which he responded well. There was no recurrence of lesion in the patient after a follow-up period of 6 months.

Conclusion

SHML may be considered a rare lesion among Nigerians. Knowledge of its clinical presentation with understanding of the differentials diagnosis is important to avoid unnecessary intervention. The diagnosis can be made from FNAC, histopathology and immune-histochemistry. There is no ideal protocol for the treatment. Follow-up is however necessary to detect relapses.

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