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Diagnosis of exclusion-cattleman disease: Our experience at atertiary care hospital

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Abstract
Aims: An overall assessment of the clinical behaviors, overall presentation and histopathological features of cases diagnosed as castleman's disease.
Materials and Methods: Clinical cases labelled as castleman's disease after excluding all other pathological processes in a tertiary care center. Were evaluated and followed A total of five cases were labelled as castleman's disease at three different sites.
Results: Out of five cases, four were seen in nodes and one was diagnosed in spleen, four cases were unicentric while one was seen to be multicentric. Each case had a different clinical presentation.one case was labelled as Plasma cell type while the other four were hyaline vascular type with one case showing abundant stroma.
Conclusion: The clinical presentations of these cases is entirely different. Each case needs a thorough work up before labelling it as castleman disease. Some of the cases may rarely show transformation to either lymphoma or sarcoma but in our cases no such thing was noted.

Keywords: Cattleman disease hyaline vascular type

Introduction
Castle-man's disease (CD), or angio follicular lymph node hyperplasia, is an uncommon condition distinguished by the development of benign lymph node masses. This condition was first described in 1956 by Castleman *et al.* [1]. It has been described mainly in case reports and series, so the true incidence and prevalence of CD is difficult. The most common location of CD is mediastinum (70%) but the involvement of extra thoracic sites like neck, axillaand pelvis have also been reported [2]. We present a case series of five cases of castleman,s disease diagnosed at three different sites over aperiod of three years and review the clinicopathlogical findings in eachcase of CD.

Case 1
A 30-year-old woman was referred to surgical oncology department of our hospital for a pelvic mass detected by ultrasonography. She denied any systemic symptoms such as pelvic pain, fatigue, fever, or weight loss. Physical examination was unremarkable and there were no swollen lymph nodes in neck, axillaries, and inguinal area. Blood tests including CA-125 showed no evidence of inflammation, infection, or malignancy. Chest X-ray revealed no abnormal findings. Ultrasonography detected 7×5-cm-sized hyperechoic mass adjacent to the Left ovary (Fig. 1A). Following computed tomography scanning of the abdomen showed a well-defined oval arterial phase ovidly enhancing lesion m 3.2x2.5 cm along the left internal illaic vessel in the pelvis,. No evidence of any surrounding stranding nodes or invasion to surrounding structures could be identified. Our laboratory received four specimen one of salpinooophorectomy,left pelvic mass, left external illaic node and omental biopsy suggesting that surgeon was suspecting an ovarian malignancy with metastasis in the nodes, Macroscopically, the pelvic mass measured 5 x 4 x 3cm in size, was egg-shaped, hard and surrounded by a thick fibrous capsule. The cut surface was homogeneous, grey white and firm (Fig 4). The histopathological examination showed that the mass consisted of hyperplastic follicles scattered in a mass of lymphoid tissue. The follicles had a characteristic expansion of their mantle zone and small germinal centers. Inside the germinal centers, marked vascular proliferation and hyalinization were observed (Fig 5).

The inter follicular stroma was characterized by moderate hyperplasia of post capillary venules and an admixture of plasma cells and eosinophil.

All the above histo morphological features favoured a diagnosis of Castleman's disease of hyaline vascular type.

Microscopy of the salpingo oophorectomy specimen was unremarkable except for a follicular cyst. Omentum and external illaic node were both unremarkable After definite establishment of the diagnosis, the patient underwent CT of the thorax in order to exclude the presence of enlarged lymph nodes in the mediastinum. As this was normal, we defined our case as an isolated Castleman's disease of the pelvis

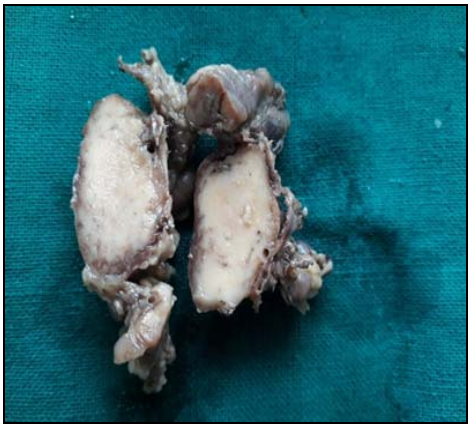

Fig 1: Gross picture of the pelvic mass. Cut section is grey white firm

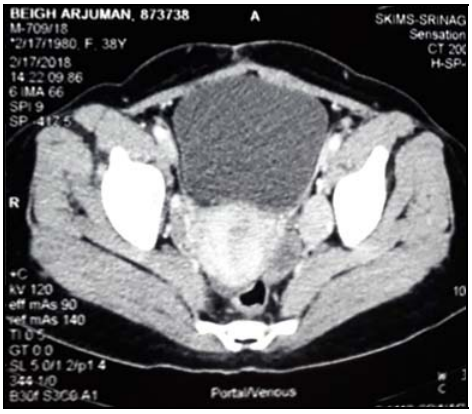

Fig 2: Computed tomography image of the patient showing the pelvic mass

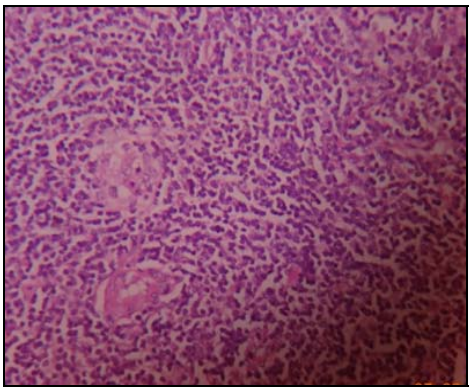

Fig 3: Photomicrograph showing prominent vascular proliferation and hyalinization of vessel walls. Mantle zone is thickened with lymphocytes arranged in layers onion skin appearance.

Case 2: Multiple Enlarged lymph nodes in the right neck were palpable in a young 25 year old female patient. Routine laboratory findings were unremarkable.FNAC was performed multiple times at various occasions but was reported as reactive everytime. Size of the lymphnode became source of worry to the physicians and a biopsy was performed.

Histological examination of these lymph nodes revealed characteristic findings, such as tight concentric layering of lymphocytes at the periphery of the lymph follicles resulting in an onionskin appearance and inter-follicular diffuse proliferation of plasma cells. The findings were compatible with CD, plasma cell type.

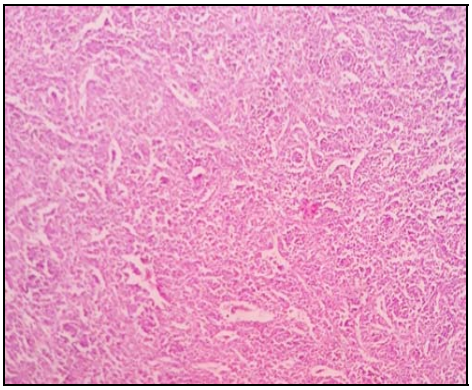

Fig 4: Photomicrograph showing sheets of mature plasma cells in the inter follicular areas

Case 3: A 25-year-old man was referred to hospital for evaluation for abdominal pain, anorexia and fever. His symptoms began a month ago.. His vital signs were as follows: body temperature 38.2, blood pressure 110/70 mmHg, pulse 84 beats per minute, and respiratory rate of 20 breaths per minute. A physical examination revealed only nonspecific findings with the exception of increased bowel sound. No lymphadenopathy was present. Laboratory results were as follows: white blood cell count 13210/mm3 (normal range 4000-8000/ mm3), hemoglobin 13.2 g/dL (normal range 14.0-18.0 g/dL), platelet count 143 × 10^3/mm3 (normal range 150-400 × 10^3/mm3), total protein 7.1 g/dL, albumin 3.6 g/dL, aspartate aminotransferase (AST) 57 IU/L, alkaline aminotransferase (ALT) 39 IU/L, alkaline phosphatase 45 IU/L, serum lactate dehydrogenase level 684 IU/L (normal range 200-450 IU/L), blood urea nitrogen 26.2 mg/dL, creatinine 1.19 mg/dL, serum sodium 133 mEq/L, serum potassium 4.0 mEq/L, chloride level 95 mEq/L, erythrocyte sedimentation rate 40 mm/h (normal range 10-20 mm/h), and C-reactive protein 11.0 mg/dL (normal}.Diagnostic laparotomy of this young man was done and some abdominal nodes with a loop of intestine resected out with suspicion of granulomatous disease,. Both the specimen where histologically unremarkable. Only benign lymphoplasmacytic infiltrate was noted in nodes and were reported as reactive. Patient was treated with antibiotics and kept on follow up with mild improvement in symptoms but present after a month with cachexia and general body weakness and hepatospleenomegaly.

The patient was operated upon and the surgeon removed spleen with wedge biopsy of liver and celiac axis nodes. we received a gross specimen of spleen measuring 18x2x6cm and weighing 700gm.sections studied from spleen showed

exaggerated white pulp with distinctive follicles and focally atrophied and regressed hyalinized germinal centers with expanded mantle zones of small lymphocytes that surrounded the germinal centers in addition to inter follicular hyper vascularity with few plasma cell, Diagnosis of hyaline vascular type of Castleman's disease was made.this was a case of multi centriccastleman. The patient is still on therapy and follow up.

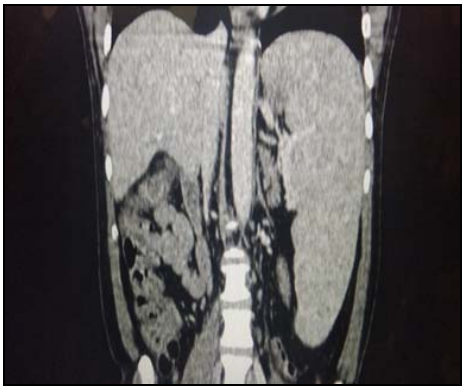

Fig 5: Computed tomography image of the patient showing splenomegaly

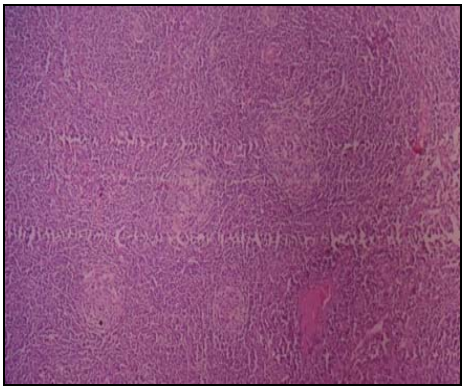

Fig 1: Photomicrograph showing atretic germinal centres traversed by penetrating vessels-Lollipop follicles

Case 4: A 30 female present with anterior neck swelling. FNAC was performed thrice at different centres. It was reported as reactive lymphadenitis with lymphohistiocytic cluster. A 3D ToF neck angio revealed well encapsulated mass lesion in left anterior triangle of neck extending to supraclavicular fossa inferior and deep to sternocleidomastoid muscle, mass lesion is abutting and indenting left common carotid artery medially. Radiologist had made a differential diagnosis of carotid body tumour and tubercular lymphadenitis

Finally the biopsy was done and we received a globular soft tissue firm mass measuring9x7x4.5 cm. Histopathology revealed thickened capsule with effacement of lymph node architecture. Prominent vascular proliferation and hyalinization of vessel walls. Prominent mantle zones with lymphocytes arranged in onion skin pattern were noted and diagnosis of cattleman's disease of hyaline vascular type was made

Case 5: A 35 year old female patient present with a lateral cervical mass in a health centre, She was referred to a hospital for fine needle aspiration. the pathologist had a difficulty in getting sufficient material and report it as benign spindle cell lesion to be confirmed on incisional biopsy. Incisional biopsy of the lesion was done', Histopathology sections revealed a spindle cell lesion showing abundant amphophillic cytoplasm with variably prominent nucleoli and lymphoplasmacyticinfiltrate, a diagnosis of inflammatory myofibroblastic tumour was made.

The whole cervical mass was excised after a month of follow up. Grossly the mass was globular and appeared to be a nodal mass with grey white firm cut surface. Histopathology sections revealed large follicles with prominent inter follicular stroma. Some cells showed spindling with atypical features both in germinal centre and in intervening tissue. Diagnosis of stoma rich hyaline vascular type of castle man, s disease was the final conclusion.

Discussion

Castleman's disease is a rare pathologic process, with undefined precise incidence and unknown etiology, characterized by lymph node hyperplasia. Although it is most commonly seen in adults, it can also occur during childhood [3]. In the vast majority of the cases, the disease is located in the mediastinum. However, extrathoracic sites have also been described, including the mesentery, axilla, neck and retro peritoneum. The disease is divided histologically in two major types: the hyaline vascular type and the plasma cell type [4]. The plasma cell type is seen in less than 10% of the patients with Castleman's disease and is characterized by a diffuse inter follicular plasma cell proliferation with minimal vascular component. The hyaline-vascular type, which is the most common type (90%) is characterized by large follicles, showing marked capillary proliferation and hyalinization in a mass of lymphoid tissue. At the periphery of these follicles there is a concentric layer of lymphocytes that comprise the mantle zone. Rarely does the mantle zone show prominent hyperplasia, while the inter follicular area presents minimal to moderate vascular proliferation and inconspicuous germinal centers.

Patients with the hyaline-vascular type of Castleman's disease are usually asymptomatic and the disease is discovered incidentally, in contrast to the patients with the plasma cell type, which are often symptomatic at the time of diagnosis. The clinical manifestations of the disease are not specific and may include fever, anemia, fatigue, weight loss. Laboratory examinations may reveal anemia, elevated erythrocyte sedimentation rate or hypergammaglobulinemia. In our case, the patient presented with a palpable abdominal mass without any other clinical sign of a symptomatic disease. However, the laboratory data showed mild anemia, leucocytosis with polymorpho-nucleosis and increased sedimentation rate. Castleman's disease can be divided into two further forms: the most common localized-solitary form and the less usual multi centric form. Approximately 80% of the cases of the solitary form belong to the hyaline-vascular type and the remaining 20% to the plasma cell type. The usual location of the solitary mass is the mediastinum (70%), whereas the pelvis is very rarely involved. The widespread form of the disease is characterized by disseminated lymphadenopathy, is almost always associated with systemic symptoms and is dominated by the plasma

cell type [6].Irrespective from the histopathological type of the disease, the localized form always shows a benign behaviour.

Complete surgical excision of the lesion - after laparotomy or even laparoscopic approach - provides cure of the disease, since there are no reported cases of recurrence after total excision of a solitary mass [7, 8].

On the contrary, the multi centric form of the disease follows a more aggressive course and is associated with poor prognosis. The therapeutic approach of the widespread form remains controversial, as many treatment regimens have been proposed, including surgery, chemotherapy, corticotherapy or combination of these [9, 10]. An accurate staging of the disease, including a very thorough clinical examination for the detection of suspicious lymph nodes in the axilla, neck or groin and CT of the thorax should be performed in any case in order to exclude the presence of extra-mesenteric disease.

The development of pelvic Castleman's disease has to be differentiated from other benign or malignant mesenchymatous lesions, such as stromal tumors, leiomyomas, leiomyosarcomas, fibromas etc.

Castleman's disease has to be differentiated also from other inflammatory lesions that may result in pelvic lymphadenopathy such as tuberculosis, metastasis from pelvic malignancy etc.

Finally, the differential diagnosis included also tumors arising from the intestine or other adjacent organs. The preoperative diagnosis of the disease is still very difficult, even with the newest medical imaging techniques [11]. Malara *et al*. [12] described in detail the sonographic, computed tomographic and angiographic features of the mesenteric Castleman's disease. According to them, the mesenteric Castleman's disease presents as a homogeneous, hypoechoic mass on ultrasound, while the color Doppler sonography reveals a vascular tumor with a low resistance flow pattern. The CT findings confirm the homogeneity and hyper vascularity of the mass and angiography demonstrates a hyper vascular mass with hypertrophied feeding vessel and a homogeneous capillary blush, at least in the hyaline vascular type [13]. Unfortunately, these radiological features are not specific for Castleman's disease, as they can beobserved in every lymphomatous tumour, benign or malignant or other mesen-teric masses [13].

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