CASE REPORTS

Retroperitoneal Pararenal Castleman's Disease

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ABSTRACT

A 51-year old male patient with a three-month history of constant and dull left flank pain was investigated by ultrasonography, computed tomography (CT) scan and magnetic resonance imaging (MRI) of the abdomen, which disclosed a 8 x 7 x 6 cm retroperitoneal pararenal mass with heterogeneous imaging characteristics and bright enhancement following intravenous contrast injection. Based on the hypervascularity of the mass and the lack of specific signs in the imaging investigation, lymphoma, sarcoma or vascular tumour were considered as probable diagnoses and the patient underwent an exploratory laparotomy. The histologic examination of the surgically resected specimen disclosed "a hyaline type of Castleman's disease". Further evaluation of the patient with antibody testing for HIV 1 and 2, as well as viral load by PCR for Herpes Virus-8 (HHV-8) were negative. Bone marrow aspiration, biopsy and immunophenotypic study did not disclose any evidence of lymphoma. Molecular study of the bone marrow for immunoglobulin heavy chain rearrangement showed a polyclonal pattern; serum protein electrophoresis did not show any evidence of hypergammaglobulinaemia and serum immunofixation electrophoresis did not show any monoclonal protein. A diagnosis of localized – unicentric type of Castleman's disease was made.

Castleman's Disease should be included in the differential diagnosis of any solitary, heterogeneous and hypervascular retroperitoneal mass. Discovery of Castleman's disease at any area of the body should be followed by a thorough imaging and laboratory work-up in order to exclude the multicentric type of the disease and the co-existence of lymphoma.

Enfermedad de Castleman de Localización Retroperitoneal Pararenal

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RESUMEN

Un paciente varón de 51 años con una historia de tres meses de dolor constante y sordo en el costado izquierdo, fue sometido a investigación mediante ultrasonografía, tomografía axial computarizada (IAC) e imagen por resonancia magnética (IRM) del abdomen. La investigación reveló una masa retroperitoneal pararenal de 8 x 7 x 6 cm, con imagen de características heterogéneas y aumento de la luminosidad tras la inyección intravenosa de contraste. Sobre la base de hipervascularidad de la masa y la falta de signos específicos en la investigación por imágenes, el linfoma, el sarcoma o el tumor vascular fueron considerados como diagnósticos probables y el paciente fue sometido a una laparotomía exploratoria. El examen histológico del espécimen resecado quirúrgicamente reveló "un tipo hialino de la enfermedad de Castleman." La evaluación ulterior del paciente con prueba de anticuerpos de VIH 1 y 2, así como la carga viral por PCR para la detección del virus herpes humano tipo 8, dio resultados negativos. La aspiración de médula ósea, la biopsia y el estudio inmunofenotípico no mostraron ninguna evidencia de linfoma. El estudio molecular de la médula ósea para el reordenamiento de la cadena pesada de inmunoglobulina mostró un patrón policlonal. La electroforesis de la proteína en suero no mostró evidencia alguna de hipergammaglobulinemia y la

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electroforesis de inmunofijación sérica no mostró proteína monoclonal alguna. Se hizo un diagnóstico de tipo unicéntrico y localizado de la enfermedad de Castleman. La Enfermedad de Castleman debe incluirse en el diagnóstico diferencial de cualquier masa retroperitoneal solitaria, heterogénea e hipervascular. El descubrimiento de la enfermedad de Castleman en cualquier área del cuerpo debe ser seguido de un examen por imágenes completo y pruebas exhaustivas de laboratorio, a fin de eliminar la posibilidad de un tipo multicéntrico de la enfermedad y la co-existencia de un linfoma.

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INTRODUCTION

In 1956, Benjamin Castleman introduced the term angiofollicular lymph node hyperplasia which described a rare atypical lymphoproliferative disorder. Clinically, the disease is classified in the localized – unicentric (LCD) and the generalized – multicentric (MCD) type, due to major differences in pathogenesis, clinical presentation, treatment and prognosis (1, 2). Histopathologically, the disease is divided into the hyaline vascular type which is more frequent in the LCD type and the plasma cell type which is more common in the MCD type (1). The localized type usually presents as an asymptomatic solitary mass whereas the multicentric type frequently shows generalized symptoms, organomegaly and lymphadenopathy and is mostly located in the peripheral lymph nodes (1, 2).

The LCD type predominantly arises in the mediastinum or the lung hilum (60–75%) and the neck (20%). Development in the retroperitoneum accounts for 10% of the reported cases while development in extremely rare locations, such as the parotid gland, has also been reported (3–6%) (3). In a recent review (4), a total of 122 retroperitoneal CD cases were reported and among them, 24 cases (20%) were located in the pararenal region. In this report, we describe a relatively rare case of LCD development in the pararenal region.

CASE REPORT

A 51-year old male patient presented with a three-month history of constant and dull left flank pain. He was initially evaluated by an internist. No abnormal clinical findings were recorded. He underwent ultrasonography, computed tomography (CT) scan and magnetic resonance imaging (MRI) of the abdomen which disclosed a 8 x 7 x 6 cm retroperitoneal pararenal mass with heterogeneous imaging characteristics and bright enhancement following intravenous contrast injection (Fig. 1. a–c).

Based on the above imaging findings, the patient was referred for further evaluation and treatment. The patient was completely asymptomatic except for the left flank pain. His previous medical history was significant for fatty liver with intermittent elevated transaminases. Two years before presentation to us, he was subjected to a CT scan of the abdomen for imaging of his liver due to his abnormal liver function tests. A retroperitoneal 2 x 3 x 2 cm mass was found then, for which no further evaluation was undertaken. His physical examination was completely normal with no lymph node enlargement or organomegaly. His complete blood

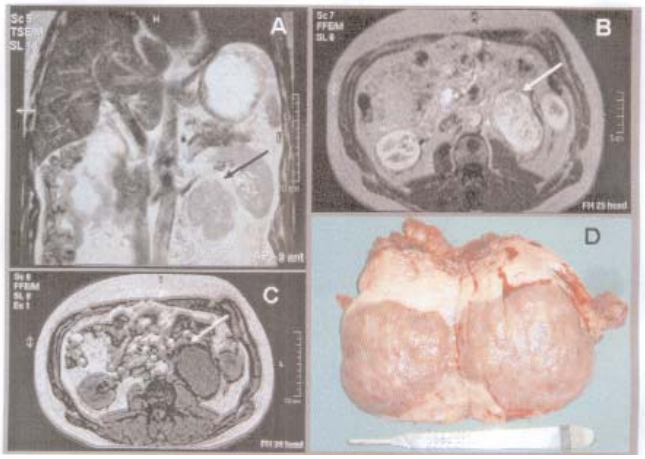

Fig. 1: (a) MRI saggital view: The location of the tumour and its relationship to the adjacent organs.
(b) MRI transverse view: Well-circumscribed mass with strong enhancement (arrow), suggesting hypervascularity.
(c) MRI transverse view: Thick vascular fibrous adhesions between the capsule of the tumour and the adjacent retroperitoneal structures.
(d) The surgically removed specimen, transversely opened.

counts and blood chemistries were within normal limits apart from slightly elevated transaminases while erythrocyte sedimentation rate (ESR) was normal. For staging purpose, a cervical and thoracic CT scan was performed but did not disclose any enlarged lymph nodes or any other abnormal findings.

Since no other involved site was found, the patient was subjected to an exploratory laparotomy through a standard midline incision. At laparotomy, an encapsulated, elliptical yellow tumour with diffuse and abundant vascularity was found in the left pararenal region. Dissection of the tumour was difficult due to thick vascular fibrous adhesions between the capsule of the tumour and the adjacent retroperitoneal structures. The surgically resected specimen measured 6.5 x 5.5 x 5 cm and weighed 180 g (Fig.1d) The patient had an uneventful postoperative course and was discharged on the seventh postoperative day.

The histologic examination of the surgically resected specimen disclosed "a hyaline type of CD" (Fig. 2). In detail, the tumour represented lymph node tissue with follicles that consisted of broad mantle zones surrounding small germinal centres with follicular dendritic cells, giving a characteristic "onion peel" appearance. Follicles were penetrated by hyalinized venules. Interfollicular areas contained a large num-

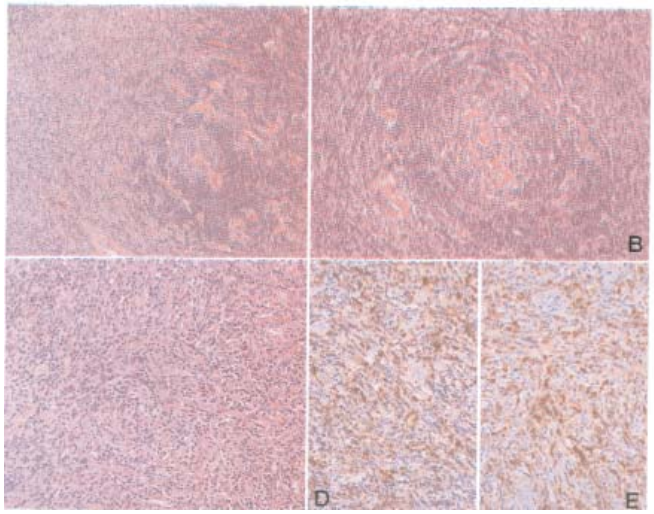

Fig. 2: Castleman's disease of hyaline vascular type, "stroma-rich variant
(a) abnormal follicles, with increased vascularity and well-developed mantle zone, increased vascularity in interfollicular areas and lack of sinuses (HE, original magnification X100);
(b) Prominent germinal centre demonstrating vascular hyaline changes (HE, original magnification X 200);
(c) Hypervascular interfollicular tissue containing large number of lymphocytes, plasma cells and plasmacytoid monocytes (HE, original magnification X200);
(d, e) Polyclonal plasma cells in interfollicular areas (d: Kappa, e: lambda, Envision, original magnification X200.

ber of lymphocytes, polyclonal plasma cells and plasmacytoid monocytes and showed capillary proliferation.

Further evaluation of the patient included antibody testing for HIV 1 and 2, as well as viral load by PCR for Herpes Virus-8 (HHV-8), which were negative. C-reactive protein, ESR and ß$_2$ microglobulin were within normal limits. Bone marrow aspiration and biopsy did not disclose any evidence of lymphoma, confirmed by a negative immunophenotypic study. Molecular study of the bone marrow for immunoglobulin heavy chain rearrangement showed a polyclonal pattern. Serum protein electrophoresis was normal, without any evidence of hypergammaglobulinemia and serum immunofixation electrophoresis did not show any monoclonal protein. The patient is now nine months post surgery and is well and without any evidence of disease. He is being followed-up at six monthly intervals.

DISCUSSION

Because of the heterogenicity, the hypervascularity and the frequent lack of the specific for CD signs (4) in the imaging investigation of a retroperitoneal mass and the fact that retroperitoneal tumours are malignant in 80% of the cases, (5, 6), CD is normally not considered in the preoperative differential diagnosis. On the contrary, lymphoma, soft tissue sarcoma or vascular tumour (7, 8) are considered as probable diagnoses. However, the present case highlights that CD should be considered in the differential diagnosis of solitary retroperitoneal masses, especially those with smoldering growth, since the mass was present in a CT scan performed two years before presentation.

In the localized type of the disease, complete and *en bloc* surgical resection of the mass is curative, with no recurrence and 5-year survival rate of nearly 100% (9).

Disclosure of CD at any area of the body should be followed by a thorough imaging and laboratory work-up in order to exclude the multicentric type of the disease, since MCD type is associated with multifocal lymphadenopathy, organomegaly, systemic symptoms, autoimmune phenomena, hypergammaglobulinaemia, hypoalbuminaemia and usually an aggressive clinical course, with concomitant or subsequent B-cell lymphoma development, immune disregulation and frequent infections (2, 10). There is an increase incidence of MCD type in recent years due to the HIV epidemic (11), thus every patient with CD should be evaluated for HIV and, whenever possible, for HHV-8. HIV-associated CD is almost always multicentric and strongly correlates to HHV-8. HHV-8 is found in 100% of HIV-associated MCD type and 40% of HIV-negative MCD type (11–13). This virus is considered to be pathogenic by encoding for a homologue of the B-cell growth factor IL-6, as well as angiogenetic factors, leading to lymphoproliferation and hypervascularity (12). Kaposi's sarcoma may be found in up to 75% of HIV positive and 13% of HIV negative patients. HHV-8 and IL-6 are not pathogenic in the localized type. Follicular dendritic cells seem to play an important role in this subtype and stromal cell malignancies have been reported in patients with hyaline vascular CD, such as follicular dendritic cell sarcoma (14). Thus LCD is rather thought as a stromal cell hyperplasia (14). The patient, in this report, was negative for both viruses.

Although lymphoma development is more common in the MCD type, lymphoma work-up should be undertaken in every patient with CD (15, 16). The index patient did not show any evidence of lymphoma, histologically, immunophenotypically and molecularly. Steroids, chemotherapy, anti-herpes virus treatment, monoclonal antibodies against IL-6 and CD20 and highly active antiretroviral therapy are treatment options for systemic CD, whereas, splenectomy might constitute the most common surgical therapeutic intervention for the correction of cytopenias. Multicentric Castleman's Disease might have a waxing and waning course, or could be very aggressive, especially in HIV-positive patients. In summary, CD should be included in the differential diagnosis of any solitary, heterogeneous and hypervascular retroperitoneal mass. Development of CD in any area of the body should be followed by a thorough imaging and laboratory work-up in order to exclude the multicentric type of the disease and the co-existence of lymphoma. If the diagnosis of localized – unicentric type of the disease is established, complete and *en bloc* surgical resection of the mass is curative, while in the generalized-multicentric type of the disease the role of surgery is limited to splenectomy for the correction of cytopenias.

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