Unicentric Castleman's Disease Radiologically Mimicking Retroperitoneal Neoplasm, A Report Of Two Cases And Review Of The Literature

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Abstract: Castleman's disease (CD) is a rare benign disorder characterized by hyperplasia of lymphoid tissue that may develop at a single site or throughout the body. CD comprises at least two distinct diseases (unicentric (localized) and multicentric) with very different prognoses. Surgery remains the main treatment for resectable unicentric CD. The two principal histologic subtypes of CD are hyaline-vascular, plasma cell variants and a mixed variant. We report two cases of unicentric Castleman's disease (UCD) treated at our institute that mimic retroperitoneal neoplasm and cured by surgical excision. We review the literature on the management of this rare entity and concentrate more on UCD.
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Key words: Castleman's disease (CD), retroperitoneal mass, unicentric Castleman's disease (UCD), Giant lymph node hyperplasia.

Introduction:

Castleman's disease was first described by Benjamin Castleman for a typical pathology of mediastinal lymph node hyperplasia then carried his name first in a case report in 1954 and later in a series of 13 patients in 1956[1,2]. Flendrig and Schillings characterized two basic pathologic types, hyaline-vascular (HV), plasma cell variants (PC) and one mixed variant of CD [3]. Keller, Hochholzer, and Castleman first used the terms hyaline-vascular (HV) and plasma-cell (PC) to describe types of CD in 1972[4]. A commonly used system to classify the heterogeneity of CD was proposed by McCarty et al in 1995 [5]lead to a distinction between the unicentric and the multicentric forms of disease. The classification correlates quite well with the histopathologically variants, as the HV type is mostly unicentric and the PC type and the mixed variant seem to be mostly multicentric[6,7]. Clinically manifestations of CD are ranging from an asymptomatic localized lymphadenopathy specially in UCD, to a severe symptomatic multifocal or generalized lymphadenopathy [8] associated with systemic symptoms and effect in the multicentric form (rarely associated with UCD) such as fever, weight loss, excessive sweating, hemolytic anemia, splenomegaly, edema and neuropathy.CD has to be treated because of its progressive course associated with local involvement of surrounding structures. Review of the literature indicates that surgery is considered to be the most adequate therapy for unicentric resectable cases of CD, as it seems to be curative in almost all of the cases.Most of the reported lesions are located in the thorax but extrathoracic involvement, including neck, axilla, mesentery and retroperitoneum, has also been reported [9].When the disease is localized in the retroperitoneum usually it has no distinctive clinical or radiological features, making it difficult to distinguish from other retroperitoneal tumors[10]. We describe two cases of Castleman's disease presented as retroperitoneal mass and review the available literature.

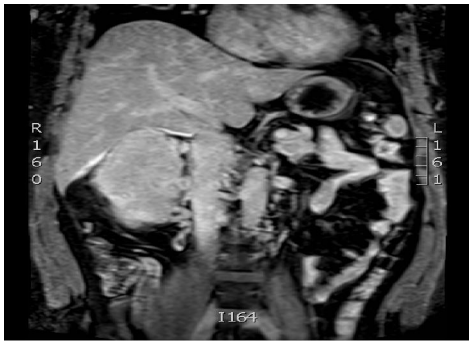
Case 1

A 46-year-old male patient who has history of recurrent urinary tract infection (UTI), and investigated in another facility in March 2012 and had US and CT scan of the abdomen, which showed incidental finding of a retroperitoneal mass. The patient was asymptomatic, he was not complaining of any abdominal pain, change in bowel habit, fever, night sweat, or history of weight loss. On examination he was in good health status, no sign of anemia or jaundice, vitals within normal, his abdomen was soft and lax with no organomegaly or palpable masses. The CT scan of the abdomen which was done in another hospital showed retroperitoneal right pararenal space mass measuring 63 x 65 x 110 mm in anteroposterior, transverse and craniocaudal dimensions respectively, not arising from adjacent solid organs, separable from the duodenum and pancreas as well as the right kidney, not arising from the supra renal gland or the liver, the lesion showed significant heterogeneous contrast enhancement, foci

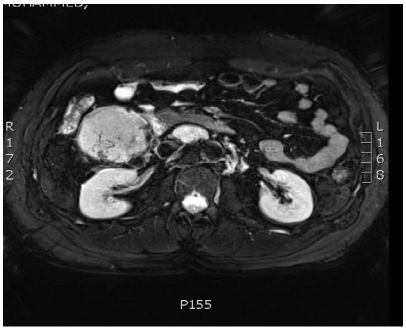
of dense calcification and lobulated outline, the lesion showed very extensive vascular channels around it, at least three arteries are coming from the aorta, two above the level of the right renal artery and one below the level of the superior mesenteric artery and above the level of inferior mesenteric artery, are seen going to the lesion, large venous structure is seen measuring about 15 mm in diameter is seen draining to the right renal vein, evidence of multiple enlarged para aortic lymph nodes. No abnormal finding in the chest, no mediastinal or hilar lymphadenopathy. In our hospital his laboratory investigations were all within normal range, with negative HIV test, MRI abdomen showed a large retroperitoneal mass seen in the right anterior pararenal space measuring 10.5 x 7.1 x 5.8 cm, showing low signal intensity on T1 and high signal intensity on T2 with early enhancement at the arterial phase. There are multiple tubular signal voids seen within this lesion which is filled with contrast in the dynamic sequence most likely blood vessels feeding this large mass. There are multiple foci of signal voids that are not enhanced, could be foci of calcification. This lesion is separable from the head of the pancreas, right adrenal, and right kidney but it is inseparable from the wall of the second part of the duodenum, and multiple retroperitoneal lymph nodes are seen (FigureS 1A, 1B). The radiological differential diagnosis includes hypervascular metastasis or Castleman's disease, as this lesion was inseparable from the wall of the 2nd part of the duodenum. Other differential diagnoses are exophytic GIST, carcinoid tumor or paraganglioma. For further evaluation a CT guided biopsy was done, which showed feature that is mostly consistent with unicentric (localized) Castleman's disease (UCD), hyaline-vascular type, HHV-8 negative. Patient underwent surgery with complete resection of the retroperitoneal mass; intra operative finding was a very vascular tumor with a very well formed pseudocapsule surrounding it, with no tumor invasion to the lateral side of the pancreas, duodenum or IVC as was suggested radiologically. Final histopathology of the resected specimen confirmed that biopsy results. Patient was on regular follow up, after a year from the procedure CT of the abdomen was repeated and it was unremarkable, and the patient is doing fine in good general condition.

Case 2

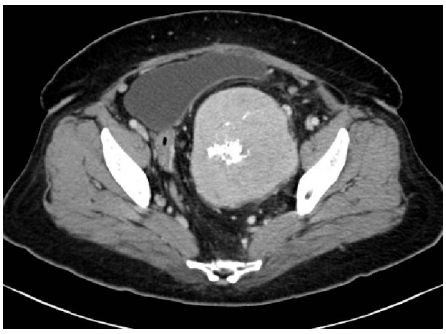
A 48-year-old female patient, known case of diabetes mellitus, presented in August 2012 with history of premenopausal bleeding and abdominal discomfort to another facility where she was investigated first by transvaginal US which showed bulky uterus and heterogeneous mass in the left side measuring 10.5x10 cm. Left ovary could not be seen. She was referred to our hospital where she was seen by gynecologist first, and on examination of the abdomen she had suprapubic tenderness, no palpable mass. Vaginal examination was positive for a hard pelvic mass felt throughout the vaginal wall. CT abdomen confirmed the presence of a large heterogeneously intensely enhancing soft tissue mass noted in the left pelvic floor and extraperitoneal in location measuring 10 x 9 x 10 cm in its maximum AP, lateral, and craniocaudal dimensions respectively (Figure 1C and 1D).Also there was a left adnexal/ovarian large cyst noted measuring 3.5 cm with minimal internal hyperdensity, could represent complex ovarian cyst with no evidence of direct invasion. It shows amorphous central calcification and multiple cystic components. The adjacent fat is preserved and it displaces the pelvic structures namely the uterus and urinary bladder anteriolaterally, with multiple enlarged lymph nodes noted in the left iliac chain as well as in the paraaortic, aortocaval, and retrocaval regions;some of which demonstrates cystic component. CT chest showed no pathologically enlarged mediastinal, hilar, or axillary lymph nodes. The radiological differential diagnosis included Castleman's disease and extraadrenal pheochromocytoma. Tumor markers in form of CA 125, CA 19-9, and CEA all were normal. So the patient was prepared for surgery, and intraoperatively there was a large mass occupying the pelvic cavity mainly in the left side measuring about 10 x 15 cm (Figure 2A).The ureter, urinary bladder, and sigmoid colon were pushed towards the right side. There was also an obvious left ovarian mass measuring about 5 x 8 cm. Complete mass resection was done with left salpingo-oophorectomy. Unfortunately, there was massive bleeding from the presacral plexus during the removal of the mass that was hard to control and the patient became hypotensive and decision was made to apply packing, and she was shifted to ICU and in 36hrs she was brought back to the OR and the packing was removed. Post-operative course was uneventful and she was discharged home in good condition. The final histopathology report of the mass was consistent with Castleman's disease, localized type, hyaline-vascular (angiofollicular) variant (Figures 2B-2D). Immunohistochemistry stain for HHV-8 was negative. The left ovary showed hemorrhagic cyst. Patient was on regular follow up for few months after surgery and she was doing fine, then she lost the follow up.



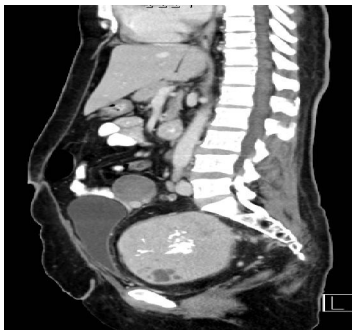
1A



1B

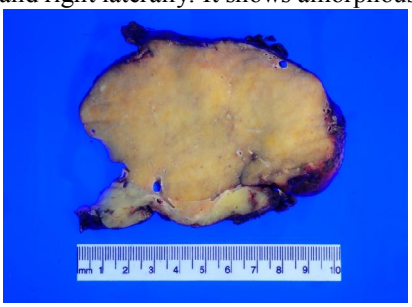


1C

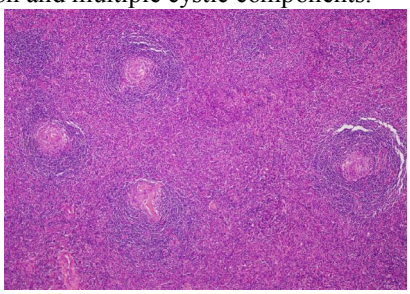


1D

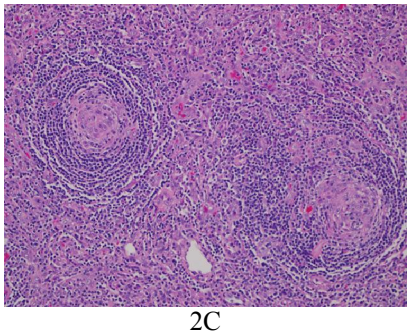
Figure 1: 1A and 1B: showed the lesion which is separable from the head of the pancreas, right adrenal, and right kidney but it is inseparable from the wall of the second part of the duodenum.
1C and 1D: showed the large pelvic mass displaces the pelvic structures namely the uterus and urinary bladder anteriorly and right laterally. It shows amorphous central calcification and multiple cystic components.



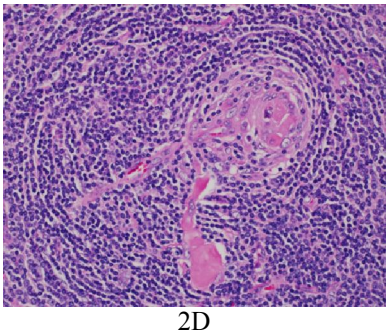
2A



2B



2C



2D

Figure 2: 2A: Gross image reveals whitish cut surface with vague nodularity.
2B: Section shows vascular proliferation in the interfollicular region with regressively transformed germinal centers.
2C: Section shows the lymphoid follicles surrounded by a tight concentric layering of the mantle-zone lymphocytes (onion- skin appearance).
2D: Section shows a sclerotic hyalinized blood vessel that penetrates lymphoid follicles radially and shows the characteristic “lollipop on a stick” appearance.

Discussion

CD is a rare disorder with undefined incidence and unknown etiology, occurring mainly in young adults, although the age may range from childhood to 66 years[11],but studies revealed age disparity between localized CD, with a median age of 20–35, and MCD, with a median age of 57[12, 13] .CD characterized by lymph node hyperplasia, while the etiology remains unclear, some authors proposed several immunological mechanisms including overproduction of IL-6 and human herpes virus type 8 infection [14], and some correlate between CD and HIV and HCV infections [15-17]. In a review done by Al-Maghrabi [18], the pathogenesis of CD was reviewed and the possible role of viruses in the development of this disease including, human herpes virus-8 (HHV-8), Epstein-Barr virus (EBV), and other viruses, was discussed and it was concluded that the HHV-8 most likely play a significant role in the pathogenesis of HIV-positive MCD, while it is less likely to play a similar role in HIV-negative CD, while the role of EBV in the pathogenesis of CD is still controversial[18-20]. Al-Maghrabi *et al.,* also concluded in another article [21] that the lymphoid cells in CD are most commonly polyclonal in origin, which supports a non neoplastic origin. However, rare cases may show lymphocyte monoclonality, which could represent the development of a neoplastic population. The latter cases should be followed closely. CD composed of three subgroups based on its histology, hyalinized vascular type (HV), plasma cell type (PC), and mixed variant. CD can be divided into two further forms on the basis of clinical criteria: the more common unicentric form and the less common multicentric form. Unicentric and MCD differ in their clinical presentation and distribution of adenopathy. From the reported literature HV type consisted of 74% of patients with UCD, and the plasma cell type was found in 33% of patients with UCD and 75% of patients with MCD [22].

The hyaline-vascular variant characterized by lymphoid follicular hyperplasia and vascular proliferation in the interfollicular region. Sclerotic blood vessels penetrate lymphoid follicles radially and impart the characteristic “lollipop on a stick” appearance[4]. The plasma cell variant characterized by sheets of polyclonal plasma cells within the interfollicular zone and more variable vascular proliferation compared to the hyaline-vascular variant.

According to the published literature, UCD was presented with asymptomatic mass in 50% of patients and symptomatic in 33% of patients [22]. Clinically, UCD tends to present in the form of an enlarged, benign, painless lymph node that generally remain asymptomatic unless it begins to compress adjacent structures or is discovered fortuitously at the time of a routine physical examination. In a review done by Al-Maghrabi [18], most of the lesions occur within the mediastinum, then in order of frequency the abdomen, neck, axilla, and inguinal region; however, CD has been also observed in many other locations including retroperitoneum, uterus, central nervous system, liver, heart, kidney, skeletal muscle, orbit, parotid, breast, spleen and lung. The pre-operative diagnosis of CD is still very difficult, with inability to differentiate CD from other tumors like lymphomatous tumor, benign or malignant, and other mesenteric masses [23]. CD is usually suspected based on combination of both imaging findings and biopsy with histopathological evaluation. CT generally shows well-circumscribed mass of soft tissue attenuation. Calcification is infrequent and can include punctate, coarse, peripheral, and arborizing patterns [24, 25]. Smaller masses show homogenous enhancement while larger masses are more heterogeneous in appearance. While differential diagnoses vary according to location but based on their intense enhancement, it includes other vascular tumors like paraganglioma, pheochromocytoma, neurogenic tumors, retroperitoneal sarcomas, desmoid tumors as well as lymphoma. Single or multiple discrete solid enhancing masses with or without calcification can be seen in the retroperitoneum, mesentery, porta hepatis, pancreas and the adnexa in the pelvis [26-29].

Treatment is often based on published case reports only, as there are no randomized trials of the therapy. Complete surgical excision is the mainstay of treatment and is virtually curative in all UCD, hyaline-vascular type cases reported so far, with a five-year survival rate approaching 100% [4, 30]. No recurrences have been reported after total excision [31–37]. However, local recurrence has been reported after subtotal or partial resection.

In conclusion, CD is a rare and poorly understood disease that created both diagnosis and therapeutic challenge for physicians and researchers. UCD is present in the form of an enlarged, benign, painless lymph node that is generally asymptomatic. The diagnosis is only confirmed by identifying characteristic pathologic features. Awareness of this disorder by clinicians and pathologists is crucial to avoid misdiagnosis and inappropriate treatment. Complete surgical removal is usually curative and results in excellent prognosis. In the light of these findings, we suggest that CD should be included in the differential diagnosis of abdominal and retroperitoneal solitary masses.

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