Case Report

Atypical presentation of Castleman's Disease as nephrotic syndrome

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Abstract

Castleman's disease is an uncommon and poorly understood disorder of atypical lymphoproliferative disorder of unknown etiology atypical. Renal manifestations, such as proteinuria, hematuria, and renal dysfunction, are common in Castleman's disease; however, a nephrotic syndrome rarely occurs.

We have encountered an unusual case of Castleman's disease characterized by nephrotic syndrome because of glomerulopathy mimicking membranoproliferative glomerulonephritis.

The diagnoses were confirmed by cervical lymph node and renal biopsy.

Key words: Castleman's disease, membranoproliferative glomerulonephritis, corticosteroids, therapeutics.

Introduction

Castleman's disease (CD) was first described in 1954 and further defined in 1956 by Benjamin Castleman. It presents with varied clinical manifestations. It is infrequently associated with renal manifestations with an underlying glomerulopathy [(1)].

According to previously reported cases, the features of renal pathology occur in diverse forms including minimal change disease, mesangial proliferative glomerulonephritis, and membrano-proliferative glomerulonephritis (MPGN), membranous nephropathy, crecentic glomerulonephritis, thrombotic microangiopathy (TMA) and amyloidosis [(2)].

There have been only reports of seven MPGN/ MPGN-like cases associated with CD, among which six reports were in the English language and indexed by the Pub- Med database[(3).]

Histologically, Castleman disease may be classified as either the hyaline-vascular or plasma cell variant, with occasional cases demonstrating mixed features. [(4)] The hyaline-vascular histology accounts for most Unicentric Castelman Disease (UCD) cases and the plasma cell type characterizes most cases of Multicentric Castelman Disease(MCD)[(4)]. UCD is typically localized, associated with minimal symptoms, and treated with local therapy alone. However, MCD is a systemic disease that commonly occurs in the setting of HIV infection and is clinically characterized by diffuse lymphadenopathy, splenomegaly, anemia, and systemic inflammatory symptoms. Accordingly, MCD is primarily treated with systemic therapies [(4)]. Although Castleman disease is not a malignant condition, the condition has been associated with an increased risk of developing certain malignancies and other diseases, most notably large B-cell lymphomas, along with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormality (POEMS) syndrome, follicular dendritic cell sarcomas, and paraneoplastic pemphigus. [(5)]

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This case report describes a 12-year-old boy with unicentric CD and nephrotic syndrome, whose mass location was (cervical and axillary region) which was resectable.

Case report

A 12-year-old male was admitted to our institution, with generalized edema.

In early 2013, he noticed a number of enlarged painless nodules in his axilla accompanied by neck swelling accompanied by progressive fatigue, pallor. Sometimes he ran a low grade fever: 37.4-37.9.

He was considered him as Castleman disease proven by cervical lymph nodes biopsy on frequent blood transfusion on need only and resection of the infected cervical and axillary lymph nodes.

During the subsequent 3-year follow-up period the patient considered to be in stable condition.

Three years later, the patient presented with recurrent peripheral edema accompanied by proteinuria and hypertension.

On examination:

He was afebrile and had pulse of 96 per minute, the blood pressure was 130/80 mmHg, and respiration was 22 per minute.

Height 130 cm (less than 3rdpercentil) .

Weight 32 kg (on 3rd percentile)

No jaundice, Skin rashes on the exposure areas Figure 1(B).

Clubbing of fingers of grade 2 .Figure1(C).

The cervical lymph nodes were enlarged, 1–3 cm in diameter, firm, mobile, and not tender.

3+Odema of lower limb.

Distended abdomen Figure 1(A), no assymmetry or skin manifestation. Hepatosplenomegaly, both soft, regular surfaces and no tenderness. Shiftinig dullness and transmitted thrill were positive Rest of the physical examination was unremarkable. Ophthalmological examination was normal.

Laboratory investigations:

- GUE: albumin 4+, RBC 20-22/HPF, Granular cast 0-2.
- 24 –hour urine for protein: volume 650 ml, protein 2840 mg/24h.
- Elevated levels of serum creatinine (Scr: 74 μmol/L).
- Blood urea 8.5 mmol/l.
- Total serum protein was 45 g/l.
- Serum albumin 18 g/l.
- CBC disclosed normocytic, normochromic anemia (hemoglobin, 9.9 g/dL), wbc 4000/l , platelet 164,000/l
- Blood film slid: dimorphic picture.64%, monocytes 3%, neutrophil 3%.
- WBC: Normal with large lymphocyte.
- Other biochemical findings were normal.
- P-ANCA, C-ANCA, ASO, RF, ANA , Anti-dsNA were negative.
- Virus markers (e. g. HBV, HCV, HIV, EBV) were negative.
- Both transferrin and total iron binding capacity were normal.
- Serum ferritin was 90 ng/ ml.
- Serum ceruloplasmin was 180 mg/dl (50 -180).
- Serum copper was 150μg/dl.
- Coombs test was negative.
- Hemoglobin electrophoresis was normal.
- Bone marrow examination was normal. Bone marrow biopsy was negative for malignancy
- Serum immunoglobulin:
- IgG 1568 g/l (710-1520).
- IgA 221.6 g/l (90-400).
- IgM 262.2g/l (75-300).
- C3 27. mg/dl (80-160).
- C4 6.4mg /dl (20-50)
- T3, T4 were normal for age.
- TSH 9.97 mlU/L (0.7-6.4).
- Liver function test normal
- Activity of lactate dehydrogenase was normal.

- Bleeding time and coagulation time were normal.
- IFAT for kala azar negative.
- Sweat test negative.
- Celiac disease screen negative

Abdominal Ultrasonography (US):

Revealed hepatosplenomegaly, lymphadenectasis in hepatic portal, neck and supraclavicular areas.

Ascites ++.

Right kidney was enlarged 11.9cm.

Left kidney was enlarged 10.5cm.

Both with ill-defined corticomedullary differentiation.

No mass.

The abdomen & chest computerized tomography (CT) with contrast:

Normal liver, enlarged in size & texture … No focal S.O.L…..no abnormal enhanced lesion.

The spleen looked markedly enlarged in size and position .

The pancrease is normal in size position, and internal structures.

Both kidneys were normal size and shape.

No abnormal mass lesion.

Both pulmonary fields look normal … no metastatic lesion.

The histological examination of a cervical lymph node biopsy:

It was compatible with the pathological findings of Castleman's disease.There is follicular hyperplasia and infiltration of the subcapsular sinuses by neutrophils and eosinophils.lypmhoid follicles are increased in number with predominance of dentritic cells within the germinal center.

A percutaneous renal re-biopsy was performed.

The specimen contained 19 glomeruli, among which 4 was sclerotic.

The renal biopsy specimen showed diffuse mesangial hyperplasia of cells. Increased matrix, glomerular basement membrane (GBM) thickening with double contours and lobulation of the glomeruli were detected.

Tubules contained occasional granular or hyaline casts. Arterioles and arteries were unremarkable. The interstitium was not infiltrated by plasma or other inflammatory cells. Immunofluorescence revealed immunodeposits for IgG (++), IgM (-), IgA (-) and C3 (+) along the capillary wall and in the mesangial area.

Congo red stain was negative.

Based on clinical and pathological features, a diagnosis of Castleman's disease accompanied with MPGN glomerulopathy was made.

The patient was treated with 6 months of corticosteroid (oral prednisolone 60 mg/SA/day for 1 month, then tapered to 40 mg /SA/ day). Corticosteroids were slowly tapered down and stopped 12 months after their initiation.

Tapering continued for 6 months but the patient had frequent relapses.

Myfortic (360 mg / day) was started.

Enalopril 5 mg /day was given also.

Thyroxin tablet for hypothyroidisim.

We are considering to start Rituximab (anti CD20 monoclonal Ab) for frequent relapsing, steroid resistant nephrotic range proteinuria.

Discussion

CD is known as a giant lymph node hyperplasia which was first described in 1956 by Castleman. CD is a rare clinicopathologic entity classified among atypical lymphoproliferative disorders [(1)].

Our patient had a classical picture of the Castelman disease. He had a cervical and axillary lymphnodes enlargement which remained localized for 3 years and resected due to infection.

He had hypothyroidism since 4 years controlled well with thyroxin.

He had a long history of illness and the nephrotic syndrome developed

Three years after the discovery of the cervical lesion. The extremely rare association between CD and nephrotic

syndrome prompted us to report this case.

Nephrotic syndrome is a very rare complication of CD. Only a few cases have been described. [6]

Other reported forms of renal involvement in CD are rare and heterogeneous and include minimal-change disease, membranous GN, membranoproliferative GN, mesangial proliferative GN and interstitial nephritis. [6]

The renal biopsy showed membranoproliferative glomerulopathy.

Although the pathogenesis of CD is entirely unknown, several investigators consider the localized plasma cell form to be an inflammatory response to an unknown antigenic stimulus. The plasma cells in the lymph node would represent an exuberant B-cell response that results in the local production of high levels of antibodies [6].

Though the renal complications caused by Castleman's disease are uncommon, there were descriptions of the role of cytokines and/or immunocomplex in the past reports of CD with renal lesions. They might play pathological roles in the development of glomerular lesions in CD. [3].

There are occasional reports about hypothyroidism associated with CD. It is more frequently found in systemic manifestations, often due to the endocrinopathy presenting in POEMS syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).[5]

In this case, we considered that hypothyroidism is an immune-mediated association with CD, although the definite specific relationship is yet unknown.

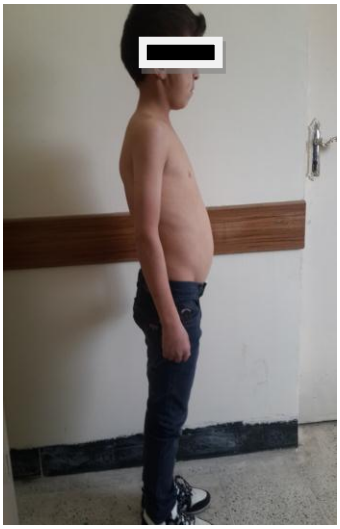
Castleman disease is a rare entity that requires a high index of suspicion, especially in the context of nephrotic syndrome management. The treatment of CD and the nephrotic syndrome are controversial issues, based essentially on case reports, since controlled clinical studies are lacking because of the rarity of the disease.[9]

In some reports, it was shown that the surgical removal of the lymph node mass was curative [8] and it led to the regression of the nephrotic syndrome [9].

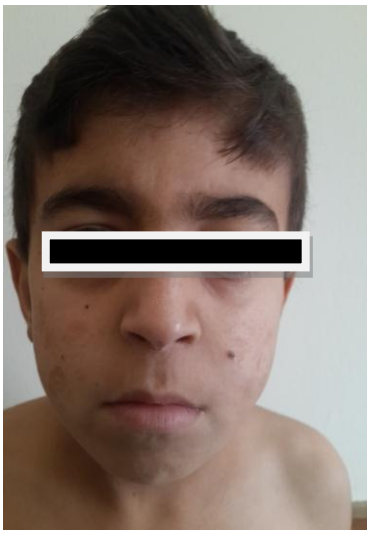
It seems that medical therapy and partial excision can be considered as an alternative to complete resection for an unresectable mass. [9].

Current approaches include high-dose corticosteroids and in some cases the addition of antineoplastic agents as, cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or cyclophosphamide/vincristine/prednisone (CVP) without rituximab has produced durable remissions. [10]

Nephrologists must remain vigilant and bring to their attention possible renal disease when encountering lymphadenopathy, in particular that accompanied by systemic syndromes.



A



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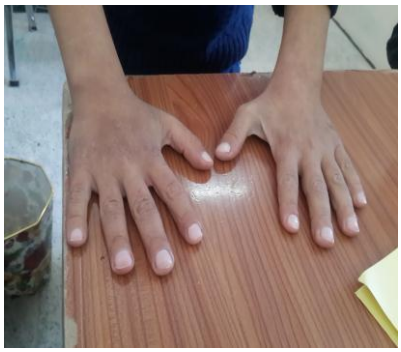

C

Figure 1 A. Notice abdominal distention in lateral view.
B. skin rash on both cheecks (sun exposure area). C.Clubbing of the fingers.

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