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Castlemans Disease – Presenting with Recurrent Pleuropericardial Effusions- Mimicking Tuberculosis

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ABSTRACT

Castleman disease (CD) is an uncommon heterogeneous group of lymphoproliferative disorders which can affect the lymph nodes of the neck, chest, abdomen and pelvis. It was first described by Castleman, in 1954, known as benign mediastinal lymph node hyperplasia, which was histologically similar to thymoma of unknown cause. [1] It is divided into unicentric (localized) Castleman disease (UCD) and multicentric (generalized) Castleman disease (MCD) based on the number of lymph nodes involved.

Castleman disease has varied presentations. Clinically it can present as localized masses, or localized lymph node enlargement. Symptoms can result from compression effects of the enlarged lymph nodes and in asymptomatic patients it can be an incidental finding on radiological imaging.

It can also present as diffuse lymphadenopathy with severe systemic symptoms . Rarely it presents with pleuro-pericardial effusions .

We present a case of a; young gentleman presenting with anorexia, weight loss and night sweats . He had large exudative pleural effusion with pericardial effusion leading to constrictive pericarditis .He was started on ATT empirically, which was later stopped due to poor response . Extensive radiological work revealed multi loculated pleural effusion and multiple lymph nodes in the axillary and cervical area . Excisional Biopsy of the lymph nodes revealed Castleman disease .

Keywords: Castleman disease , pleural effusion , Multi centric disease , human herpes Virus 8, multicentric disease.

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Introduction

Castlemans disease was described in 1950 s by Castleman et al , as a rare haematological disorder which was initially described as affecting lymph node at a single location[2]. However in 1980s a large number of cases were reported involving lymph nodes at multiple sites [multicentric castle -man disease] [3] .Multi centric Castleman disease in 44-66% cases is associated in immune compromised patients with human herpes 8 virus infection [4]

MCD is further classified as idiopathic MCD [iMCD], human herpes virus-8 [HHV8]-associated MCD [HHV8-MCD] usually associated with an HIV infection and [POEMS]-associated MCD [POEMS-MCD] [polyneuro-pathy, organomegaly, endocrinopathy, mono-clonal plasma cell disorder, skin changes][3]

Clinically iMCD- is further classified as a) iMCD-TAFRO [thrombocytopenia, anasarca, fever, reticulin fibrosis[of the bone marrow], and organomegaly] [4] γ-globulin levels are normal .b) iMCD-NOS [not otherwise specified]. c) IPL [idiopathic plasmacytic lymphadeno-pathy].

Histologically, iMCD is sub classified as : plasma cell and hyper vascular types [4]. The mixed type shows features of of both the above subtypes, but there is no clear pathological definition [3]

iMCD-TAFRO histo- pathologically associated with the Hyper vascular type, and iMCD-NOS usually associated plasma cell type[3]

iMCD-NOS is associated with un- diagnosed, atypical autoimmune diseases, also in [5] conditions causing hypergammaglobulinemia such as infections, hepatitis, collagen diseases, hyperthyroidism, allergic diseases, liver cirrhosis and lymphoma [6]

A comprehensive battery of tests is required to diagnose i-MCD namely tests for organ dysfunction [example renal functions, LFT, ECHO, pulmonary function tests] and inflammatory markers [complete blood picture, ESR]. Pan CT to visualize the extent of disease is indicated. PET scan is an alternative if diagnosis like lymphoma needs to be excluded .Auto- immune profile , detailed virology work up including HIV serology , HHV-8 pcr in peripheral blood , EBV igG and IgM are needed. Bone marrow is needed to rule out multiple myeloma ,Monoclonal gammopathy of unknown significance and reticulin fibrosis. Cytokine profile including IL-6 and VEGF to be done . Finally excisional biopsy of the lymph node will give definite diagnosis [7].

Criteria for severity include evidence of organ dysfunction such as renal failure, severe anaemia, generalized anasarca and pulmonary dysfunction resulting in poor performance requiring critical care. Laboratory features include elevated C- reactive protein levels [≥100 g/dL], severe hypoalbuminemia [≤2.0 g/dL], and thrombocytopenia [≤100 × 10^{12}/L]. Patients with lymphocytic interstitial pneu-monitis, if not treated properly can progress to end-stage pulmonary fibrosis [7]

CASE DESCRIPTION:

38-year-old Syrian gentleman, with no known medical comorbidities presented to our hospital with history of shortness of breath and pleuritic chest pain . He was found to have right sided loculated pleural effusion and was admitted for pleural tapping and detailed work up.

One year back , he presented to a private hospital with progressively increasing shortness of breath. He was found to have bilateral pleural effusion. Pleural tapping was tried but failed. Sputum AFB was negative but based on clinical suspicion , he was empirically started on ATT . There was transient improvement in symptoms .He continued to have drenching night sweats, low grade fever and weight loss of >30 kg over a period of 6 months . He had no history of contact with tuberculosis or exposure to asbestosis or any other industrial agent. He was a non-smoker .

Patient was re-admitted to another hospital facility .Chest xray revealed massive right sided pleural effusion . Blind pleural aspiration was tried ,it failed . Patient had episodes of paroxysmal atrial fibrillation. Echocardiogram

revealed mild pericardial effusion and features of constrictive pericarditis. Only 10ml of pericardial fluid was aspirated , which was exudative in nature , micro and culture revealed no growth.

Patient was continued on ATT and advised close follow up in medical clinic. 4 months later, he was advised to stop ATT since he continued to have spikes of low grade fever .All investigations [including sputum AFB smear and culture , T spot] were negative . Patient continued to have persistent pleural effusion for which he went to multiple clinics and then finally came to our hospital

At admission to our hospital he had normal vitals ,[pulse 92/min , afebrile , saturation 96% on room air] . There was no signs of pericardial tamponade or heart failure .There were no skin lesions.

On examination of chest; there were decrease breath sounds right base with crepts . Cardiovascular examination : normal intensity of heart sounds [there was no pericardial knock] and mild hepatomegaly could be appreciated on abdominal examination .

He was found to have a loculated right sided pleural effusion. Ultrasound pleural cavity revealed multi septate right sided pleural effusion with low level internal echoes suggestive of an exudative effusion. Drainage was attempted by interventional radiologist under ultrasound guidance.

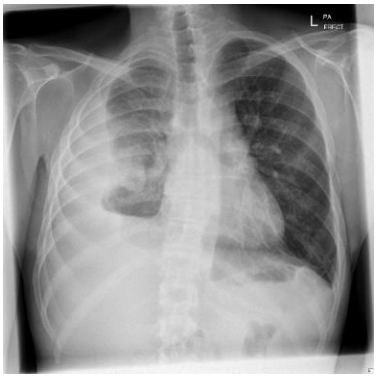


Fig- 1 Chest xray [at admission to our hospital]showing moderate right sided pleural effusion.

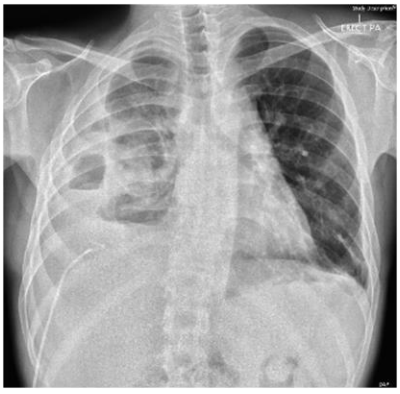


Fig-2 [persistent right sided pleural effusion even after drainage – multiple air fluid levels are seen .There is hydro-pneumonthorax

Pleural fluid analysis revealed an exudative effusion , fluid micro and culture revealed no growth and cytology was negative for malignant cells. AFB smear and culture , pleural fluid de-aminase were negative for tuberculosis.

Baseline investigations during admission were as follows[table- 1]

Blood Investigations	Value	Reference range
Haemoglobin, Blood	11.1	13.0 – 17.0 g/dL
Wbc count	13,000 /ul	4,000- 11,000 /ul
MCV	71.1	77.0 – 95.0 fL
MCH	23.3	27.0 – 32.0 pg
Platelets	175,000/ul	150,000-450,000/ul
Creatinine Blood	0.5	0.7 – 1.2 mg/dL
ESR	52	<11
C-reactive Protein Blood, Venous	33.1	<5.0 mg/L
NT-proBNP	388	<125 pg/mL
Prothrombin Time	13.6	9.7 – 11.4 sec
INR	1.32	0.8 – 1.1
APTT	36.6	27 – 40 sec
Liver Function Test		
Bilirubin, Total	0.6	0 – 1.0 mg/dL
Alkaline phosphatase	192	40 – 129 U/L
SGPT [ALT]	10	0 – 41 U/L
Total protein /	7.6	6.6 – 8.7 g/dL
Albumin	3.4	3.4 – 4.8 g/dL
Globulin	4.3	2.8 – 3.4 g/dL
T-SPOT Tuberculosis Test Blood, Venous	NEGATIVE	NEGATIVE
Hepatitis B surface antigen Blood, Venous	NON – REACTIVE	NON - REACTIVE
Hepatitis C Antibody Blood, Venous	NON – REACTIVE	NON - REACTIVE
HIV antigen and antibody Blood, venous	NON – REACTIVE	NON - REACTIVE
Sputum AFB smear and culture	No AFB seen	No AFB seen
Human herpes virus 7 and 8	Pcr [peripheral blood]	negative
EBV [ebstien barr virus]	Ig G and Ig M	negative

The drained fluid was sent for further investigations as listed below. [fig 2]

Pleural Fluid Cell Count	Value	Reference Range
Colour	Orange	Colourless
Appearance	Slightly turbid	Clear
Total nucleated cell count	223	<1000 cells/mm^3
Differential count		
Neutrophils	68	< 25 %
Lymphocytes	22	< 75 %
Monocytes	10	%
Eosinophils	0	%
Other cells	0	%
Differential Comments	Macrophage and mesothelial cells seen in the film	
Protein, Fluid	4.7	>= 3 g/dL Exudate < 3 g/dL Transudate
Glucose, Fluid	74	65 – 140 mg/dL
LDH, Fluid	277	U/L >2/3 of serum value – exudative
Pleural Fluid Adenosine deaminase	4	0 – 30 U/L
AFB smear and culture	No acid-fast bacilli isolated	No acid-fast bacilli isolated
TB PCR Direct Detection for Fluid	M. TUBERCULOSIS COMPLEX NOT DETECTED	M. TUBERCULOSIS COMPLEX NOT DETECTED
Pleural fluid cytology	NEGATIVE FOR MALIGNANCY	

CT chest with contrast was done which showed right sided pleural effusion looking like empyema and lymphadenopathy involving multiple sites .CT abdomen pelvis with contrast showed hepatosplenomegaly. No retroperitoneal lymphadenopathy could be appreciated.

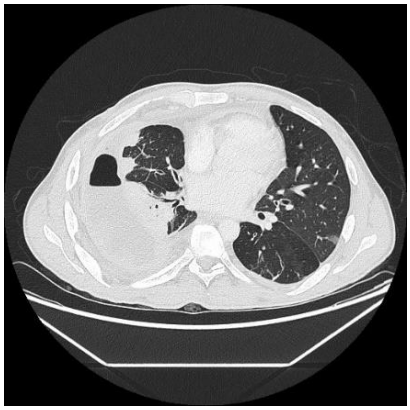


Fig1

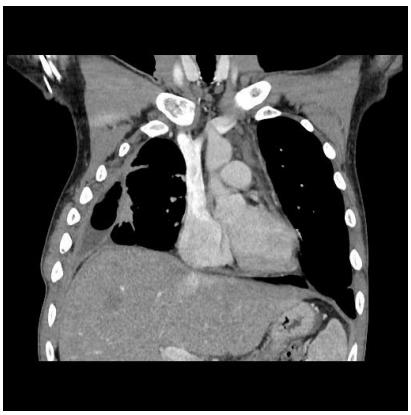


Fig 2

Figures 1 and 2 CT chest with contrast showed thick walled marginally enhancing encysted right sided pleural effusion, enlarged right supra clavicular, right axillary , anterior mediastinal , prevascular , cardio-phrenic and retrocaval lymph nodes.

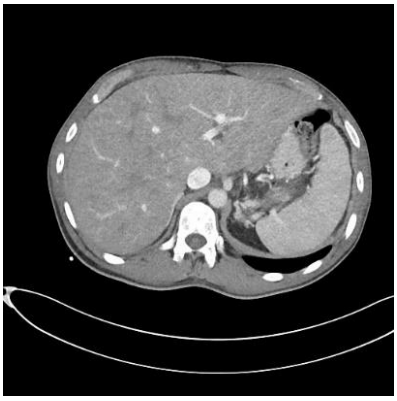


Figure 3 : CT abdomen pelvis with contrast showed diffusely enlarged liver with fatty changes, enlarged spleen with no retroperitoneal lymphadenopathy.

Echo cardiogram: [trans-thoracic]

Normal left ventricular size [LVEDD= 3.9 cm

Normal left ventricular systolic function [EF between 55-60%]

Septal bounce is present – consistent with constrictive peri-cardiites

Diastolic filling pattern is normal for patient age

No evidence of pulmonary hypertension

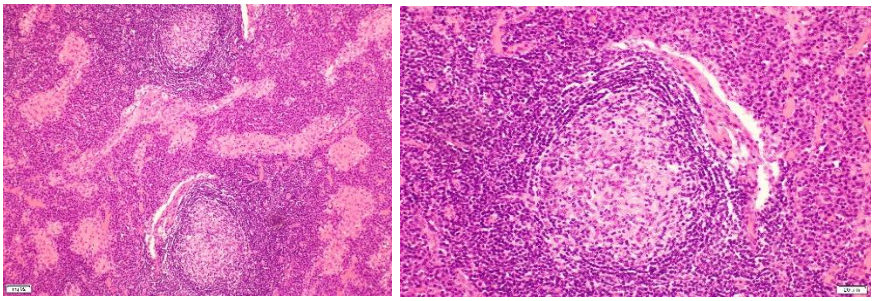
Possibility of constrictive pericarditis – CT chest is recommended .

Lymph node biopsy

An excisional lymph node biopsy was taken from the right cervical lymph node and the report was consistent with Castleman disease of the plasma cell type variant.

Immunohistochemistry performed on the lymph node showed the following:

CD20 highlights the reactive B lymphocytes, CD3 highlights the reactive T lymphocytes. CD38 highlights the numerous plasma cells in the interfollicular area. Both Kappa and lambda are expressed. HHV-8 [repeated] is negative. Ki-67 proliferation index is low.



[Fig 4 and fig 5]

[Figures 4 and 5 Showed lymph node showing expansion of interfollicular areas by sheets of plasma cells with preserved sinus and active germinal centre. Onion skinning of lymphocytes is also noted.

Patient was referred to haematology . He was discharged from the hospital with early out - patient follow up with cardiothoracic surgery to plan for thoracotomy/decortication.

The following labs were done as a part of the work-up from haematology. Autoimmune profile [including Anti- nuclear factor and anti- DS DNA] were negative. [Figure 3]

	Value	**Reference range**
Serum immunofixation	No monoclonal gammopathy detected	
Direct coombs test	Direct Antiglobulin Test is positive [+2]. DAT Monospecific IgG Positive [+1]. Complements Negative.	
Protein Electrophoresis [Serum]	No paraprotein band is detected. Polyclonal increase in gamma globulins.	
Immunoglobulins		
IgG	23.37	7.00 – 16.00 g/L
IgA	3.27	0.70 – 4.00 g/L
IgM	1.57	0.40 – 2.30 g/L

He was discharged from the hospital with early out -patient follow up with cardiothoracic surgery to plan for thoracotomy/decortication. Patient subsequently

had a right posterior -lateral thoracotomy and decortication and partial pleurectomy. Pleural biopsy revealed thickened fibro collagenous tissue with marked haemorrhage and necrosis, scattered spindle cells and many lymphoid aggregates were seen with few sider phages and no evidence of granuloma or malignancy was identified.

Pt was discharged with early cardiology appointment , for Cardiac CT and to decide about cardiac catheterization for constrictive pericarditis.

He was started on prednisolone 50mg daily by haematologist . The fever and constitutional symptoms showed gradual improvement . Patient was given early follow up in haematology clinic but was lost to follow up

Discussion

Castleman disease is also known as giant lymph node hyperplasia , angio follicular lymph node hyperplasia; and at times Castleman's lymphoma. [7]. Several anatomical sites can be involved , namely mediastinum [67%], neck [14%], pelvis [4%], and axilla [2%],[7] . It effects

patients of all ages and and all genders equally . [8]

Histologically there are 2 distinct types . 80% cases are Hyaline-vascular type these patients are frequently asymptomatic, whereas the plasmacytic variant is less common [20%]. Patients with plasma cell type present with systemic symptoms, such as weight loss fatigue , and lymph node enlargement. Our patient , had plasma- cell type variant .He also had more B symptoms Only 20% of the plasma cell type present with mediastinal mass.[1]

CD infrequently manifests as multicentric, or systemic disease [usually the plasmacytic variant] accompanied by systemic involvement of the peripheral lymphoid tissue, hepatosplenomegaly, fever, and night sweats.[8]

Our patient has Castleman syndrome-i- MCD, plasma cell type .He presented with large size loculated pleuro- pericardial effusion later causing constrictive pericarditis . Pleural effusion is a rare manifestation of Castle man disease. [9] It was found in only 2 of 81 cases reported by Keller et al [9] .The pleuro-pericardial effusions and symptoms of fever, malaise [as in our patient] are due to hyper-cytokinemia especially elevated levels of interleukin -6 .[9] . Elevated interleukin-6 levels also cause hypergammaglobulinemia and thrombocytosis , but less extreme anasarca. The TAFRO subtype often are more symptomatic and have worse outcome.[6]

MCD clinical presentation ranges from mild constitutional symptoms to life-threatening cytokine storm and organ failure [4].Our patient had moderate to severe constitutional symptoms but there was no evidence of life-threatening cytokine storm and organ failure. Also he had normal platelets and mildly elevated gamma globulin levels.

Criteria for severity in iMCD include: [if they met at least two of the following five criteria]: Eastern Cooperative Oncology Group performance status ≥2; stage iv renal impairment [estimated glomerular filtration rate <30; creatinine >3.0]; pleural/pericardial effusion, ascites , anasarca. Effects of hyper-cytokinemia or low albumin; haemoglobin ≤8.0 g/dL; and pulmonary involvement or interstitial pneumonitis causing dyspnoea.[7]

Patients who satisfy less than two criteria were considered to have non severe i-mcd [7]. Our patient only fulfilled one of the criteria , hence had evidence of non- severe i-mcd. The paroxysmal episodes of atrial fibrillation in our patient were due to constrictive pericarditis . The aetiology of CD is still unknown. Viral infections like human herpes virus 8 and Epstein-Barr virus play an important role . It is postulated that these agents induce B lymphocytes proliferation which are present in the [cortical] mantle area of lymph nodes to produce interleukin-6 [IL-6]. The increased IL-6 expression by viral antigens of human herpes virus 8 in plasma cytic variant of i- mcd supports a viral aetiology [10].

VEGF [Vascular endothelial growth factor] causes angiogenesis . Immunohistochemical studies show a high expression level of VEGF in plasma cells of the interfollicular region in patients with Castleman disease . The extensive vascularization observed in CD , is supportive of the possibility that vascular endothelial growth factor participates in the physiopathology of the disease[11].

The TAFRO patients have highly vascular lymph nodes and have elevated Vascular endothelial growth factor levels [VEGF]. Interleukin 6 is only mildly elevated. [3]

In setting of HIV infection , CD can be fatal .HHV-8 can be detected in the plasmablastic cells is considered to be a causative agent , 27[12]. The clinical course of MCD is manifested by recurrent attacks, with systemic symptoms, lymphadenopathy, splenomegaly, cytopenia, and inflammation associated with high HHV-8 viral load in the peripheral blood mononuclear cells[12] HHV-8-associated latent nuclear antigen-1 [LANA-1] is also present [13].

Radiologically thoracic CD manifests as a rounded solitary mediastinal or hilar mass in asymptomatic individuals . Differential diagnosis

of mediastinal CD includes thymoma, lymphoma, or neurogenic tumour . Hilar CD may simulate bronchial adenomas . Rarely thoracic CD can arise from other locations, including the pleura, pericardium, intercostal space, and lung. Pleural CD may present as a well-defined interlobar mass or massive pleural effusion [14] Pericardial CD may present as a pericardial mass looking like a pericardial cyst [15]. Intercostal CD may manifest as an extrapulmonary mass with rib erosion [16]

MCD can present as diffuse reticulonodular infiltrates , ascites with hepatosplenomegaly. [17]

In one study it was found that age > 40 years, Plasma cell variant, hepatomegaly and/or splenomegaly, haemoglobin <80 g/L, and pleural effusion are significant risk factors for reduced Overall survival in iMCD [18].

There are multiple modalities for treatment of CD. Steroids should not be started as a monotherapy for Castleman disease .Glucocorticoid monotherapy for iMCD is reported to provide only mild symptom relief and incomplete remission with frequent relapses during steroid tapering, is seen. [19]

Castleman disease collaborative network , established in 2013 put forward guidelines for diagnosis and treatment of Castleman disease . These guideline recommends an anti-IL-6 monoclonal antibody, siltuximab, with or without corticosteroid as the first-line therapy for i-MCD regardless of disease severity.[20] Tocilizumab, a monoclonal antibody against IL-6 receptor, is also recommended as an alternative if siltuximab [21] is not available. Corticosteroid monotherapy is not recommended because of its high treatment failure rate and frequent relapses.

Initially after watchful waiting our patient was initially started on steroid monotherapy .As in our case the use of corticosteroids, alone, may best be reserved as a temporary intervention in acute situations where more definitive therapy has not yet been decided or will be delayed. In our patient bone marrow exam was not done because all cell lines in the full blood count and peripheral film were normal .

Our patient was given close follow up in haematology clinic , with meticulous monitoring of symptoms and lab parameters to decide about starting further therapy but he was lost to follow up.

Conclusion

Castle man disease [i-mcd sub type] should be considered in the differential diagnosis of all chronic , exudative pleuro-pericardial effusions with multiple lymphadenopathies and B symptoms .

If a patient is empirically started on ATT , for exudative pleural effusions . Clinicians should consider holding ATT after 4 – 6 weeks if there is no clinical improvement.

Abbreviations:

1) CD-Castle man disease
2) i-MCD [idiopathic multicentric disease]
3) ATT [Anti tuberculous treatment]

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