

# Castleman's disease as a rare differential diagnosis of lymphadenopathy: 2 case reports and review of literature

## Abstract

**Introduction:** Lymphadenopathy is a common complaint in children. It's defined as abnormality in size or character of lymph node. It may be localized or generalized. It may be part of a group of signs and symptoms or the sole finding and chief complaint. Several reasons can lead to Lymphadenopathy. Castleman's disease is a rare differential diagnosis of generalized or localized Lymphadenopathy. It's a rare lymph proliferative disorder that rarely occurs in children.

**Case presentation:** We reported two cases, the first one was 13years old female with multicentric castleman's disease associated with constitutional manifestations and unusual hyaline vascular pathology successfully treated with monthly combination chemotherapy, the second one was 2.5years old male with unicentric hyaline vascular castleman's disease with unusual young age at presentation successfully treated with surgical excision.

**Conclusion:** Castleman's disease is a rare cause of Lymphadenopathy. Although, it's rare in children, it can occur at any age. Most of cases of multicentric castleman's disease are plasma cell variant, yet hyaline vascular type may occur. Multicentric castleman's disease can be successfully treated with monthly combination chemotherapy. Most cases of unicentric castleman's disease are hyaline vascular type. Although, surgical removal of unicentric type is usually sufficient to achieve complete remission, recurrence can still occur.

**Keywords:** lymphadenopathy, castleman's disease, hyaline vascular, plasma cell, CD

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**Amany M Ali, Heba Abdel-Razik Sayed, Mahmoud M Mohammed**

Department of Pediatric Oncology, South Egypt Cancer Institute, Egypt

**Correspondence:** Mahmoud M Mohammed, Department of Pediatric Oncology, South Egypt Cancer Institute, Assist University, Egypt, Tel: +201146703107; Email elzimbily@aun.edu.eg

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**Abbreviations:** HHV-8, human hepes simplex virus type 8; HIV, human immunodeficiency virus; SECI, South Egypt cancer institute; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DNA, deoxyribonucleic acid; CT, computerized tomography; LDH, lactate dehydrogenase; CD, castleman's disease

## Introduction

Lymphadenopathy is a common complaint in children. It's defined as abnormality in size or character of lymph node. It may be localized or generalized. It may be part of a group of signs and symptoms or the sole finding and chief complaint. Several reasons can lead to Lymphadenopathy.<sup>1</sup> Castleman's disease (CD) is a rare differential diagnosis of generalized or localized Lymphadenopathy. It's a rare lymph proliferative disorder characterized by enlarged hyperplastic lymph nodes with vascular proliferations of uncertain cause. It's most commonly seen in adults but: it can also occur in children.<sup>2</sup> Castleman et al first described this disorder as a benign localized enlargement of hyperplastic lymph nodes.<sup>3</sup> Flendrig et al also described 2 separate histo-pathological types of castleman's disease on 1970.<sup>4</sup> Historically: castleman's disease was classified according to the extent of lymph node involvement into unicentric and multicentric types. Recently: histopathogenetic classification of castleman's disease is favored. The histopathogenetic classification distinguishes between hyaline vascular castleman's disease (HV-CD): plasma cell castleman's disease (PC-CD): mixed type: human herpes virus 8 (HHV- 8)-associated castleman's disease and multicentric castleman's disease not otherwise specified.<sup>5</sup>

The pathology of hyaline vascular castleman's disease is characterized by lymphoid proliferation with depletion of the germinal

center and expansion of the mantle zones. Small lymphocytes are arranged concentrically giving "onion-skin" appearance.<sup>6</sup> The pathology of plasma cell type is characterized by preservation of the nodal architecture with follicular hyperplasia. Intermolecular area shows abundance of plasma cells.<sup>7</sup> Plasma cells are usually polyclonal but may be monoclonal if it's associated with POEMS syndrome<sup>8</sup>. Human herpes virus 8 (HHV-8) associated Castleman's disease is associated with immunodeficiency. Pathologically: the involved lymph nodes are characterized by large number of immunoblasts (or plasmablasts) in the outer mantle zone of some follicles. Immunoblasts are polyclonal with weak expression of CD20 [9]. We report 2 cases of Lymphadenopathy that was diagnosed finally as castleman's disease. The first is of generalized Lymphadenopathy with constitutional manifestation diagnosed finally as castleman's disease. Patient received combination chemotherapy with long survival. The second case is of recurrent localized Lymphadenopathy diagnosed as castleman's disease with unusual very young age presentation. Surgical removal of the mass was done with long survival.

## Case presentation

### First case

A 13years old female child was referred to Pediatric Oncology Clinic at South Egypt Cancer Institute (SECI) as a suspected case of lymphoma with a one month history of high grade fever mainly by night associated with itching: night sweating and gradual progressive loss of body weight. Twenty days ago: she developed bilateral ankle pain and swelling not associated with trauma. Fifteen days ago: she developed puffiness of eyes: painful abdominal distention and bilateral leg swelling associated with bilateral axillary and cervical

swellings. The child had no family or past medical history of note. Examination of the child revealed poor general condition with cachexia {weight=32kg less than 5% of weight for age according to official 2000 center for disease control and prevention (CDC) growth charts: created by the National Center for Health Statistics}: severe pallor: puffiness of the eyes: respiratory distress 6/10: marked decrease of air entry on the right side of chest: diffuse abdominal tenderness and rebound tenderness: positive shifting dullness with hepatomegaly about 5cm below costal margin: bilateral pitting lower limb oedema and generalized painless Lymphadenopathy.

Laboratory Investigations (Table 1) revealed moderate normocytic normochromic anaemia with normal reticulocytic count: hypoalbuminemia with normal 24-hours protein collection in urine: raised acute phase reactants (Erythrocyte sedimentation rate "ESR" and C-reactive protein "CRP"): normal anti- nuclear antibody: anti double stranded DNA: rheumatoid factor and negative tuberculin test. Human immunodeficiency virus (HIV) serology was negative at presentation. Chest X-ray showed moderate right sided pleural effusion. Computerized tomography (CT) neck: chest and abdomen showed multiple enlarged cervical lymph nodes 1.5\*1cm: enlarged bilateral axillary lymph nodes the largest one 2\*3cm: multiple enlarged anterior mediastinal lymph nodes 2.5\*2.5cm: moderate right sided pleural effusion: left lower lung lobe pneumonic consolidation: mild hepatomegaly and moderate free ascitis (Figure 1). Excisional biopsy of an axillary lymph node (Figure 2) was performed and histopathological examination revealed hyaline vascular Castleman's disease ( increased number of follicles with atrophic germinal centers and the inter follicular area showing proliferation of hyalinized capillaries and thick wall blood vessels). Child received adequate supportive care and CHOP regimen as a combination chemotherapy {cyclophosphamide 1000mg/m<sup>2</sup> (d1): vincristine 1.5mg/m<sup>2</sup> (d1): doxorubicin 40mg/m<sup>2</sup> (d1): prednisolone 40mg/m<sup>2</sup> (d1-d5)}. After 3 cycles of CHOP: there is marked clinical improvement with disappearance of constitutional manifestations: lower limb oedema: ascitis: pleural effusion and puffiness of the eyes.

**Table 1** Laboratory investigations on admission to South Egypt Cancer Institute and after 6 CHOP cycles of the 1<sup>st</sup> case

On admission	After 6 CHOP cycles (at the end of treatment)
Hemoglobin 7.8g/dl	Hemoglobin 11
White Cell Count 4* 10 <sup>9</sup> /l	White Cell Count 3.6*10 <sup>9</sup> /l
Neutrophil 25%	Neutrophil 75%
Platelet 381*10 <sup>9</sup> /l	Platelet 249
ESR 1st hr 102 2nd hr 130	ESR 1st hr 5
Albumin 20g/l	Albumin 37g/l
ALT 27U/l	ALT 18U/l
AST 73U/l	AST 34U/l
Bilirubin Total 0.19mg/dl	Bilirubin Total 0.18
Urea 16mg/dl	Urea 23mg/dl
C-reatinin 0.5mg/dl	C-reatinin 0.3mg/dl
C-reactive protein 140mg/l	C-reactive Protein Normal
HIV, HBV, HCV Serology -ve	

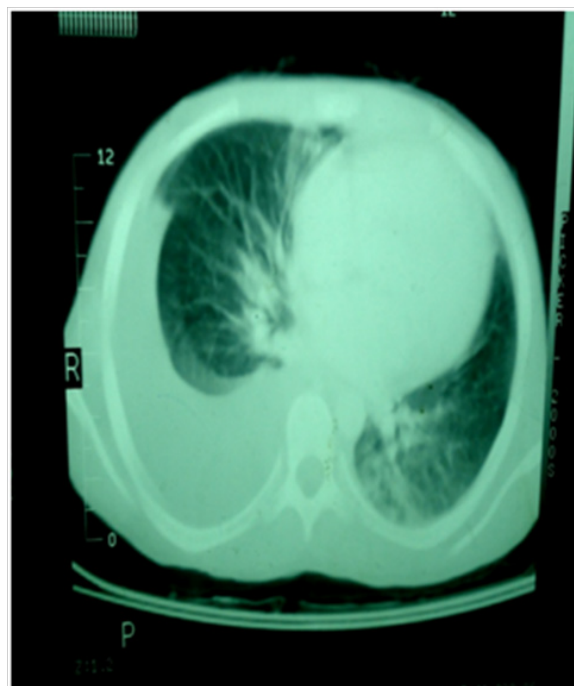
The child gained weight to be 36kg within 4 months of treatment which correlates with the 10% of weight for age according to CDC growth charts. Laboratory investigations became free. CT neck: chest and abdomen showed bilateral enlarged deep cervical LNS largest 0.7\*1.2cm: disappearance of the previously seen right sided pleural effusion: reduction of the previously seen mediastinal: axillary

Lymphadenopathy to be 1\*1.6cm and disappearance of the ascitis. Child then received another 3 cycles of CHOP. On finishing treatment laboratory investigations continue to be within the normal range and CT neck: chest and abdomen revealed only bilateral nonspecific cervical lymph nodes enlargement: the largest one was 1 cm with disappearance of the previously described enlarged axillary and mediastinal lymph nodes. She is now on regular follow-up for 48 months with complete clinical and radiological remission.

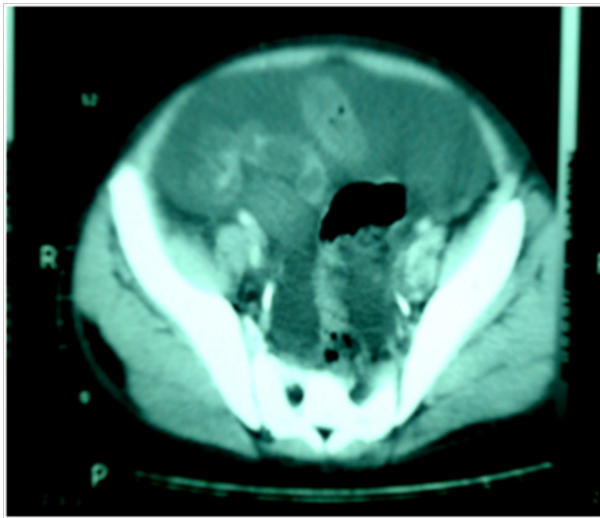


**Figure 1** Radiological findings at presentation.

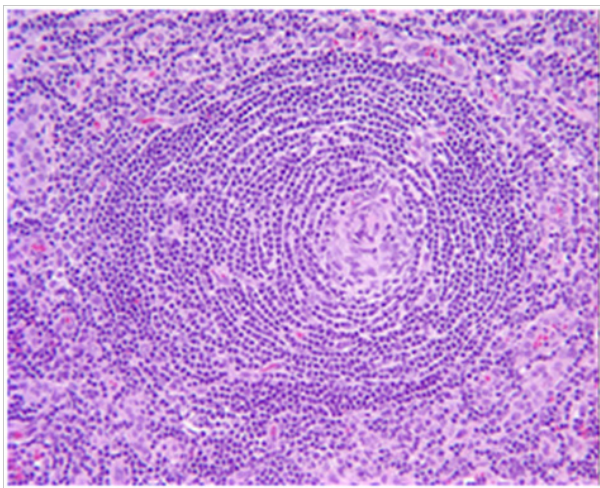
**Figure 1a** Chest X-ray showing moderate right sided pleural effusion.



**Figure 1B** Chest showing right sided pleural effusion.



**Figure 1C** CT abdomen showing moderate free ascitis.

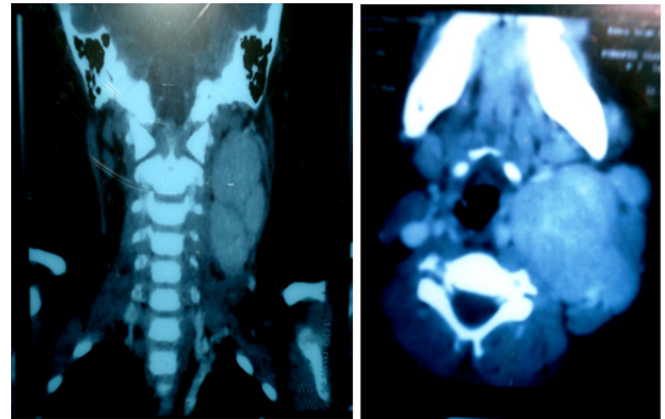


**Figure 2** Histopathological picture of axillary lymph node showing hyaline vascular castleman's disease with increase number of follicles, atrophic germinal centers, the intermolecular area showing proliferation of hyalinized capillaries and thick wall blood vessels.

## Second case

A 2.5years old male child was referred to Pediatric Oncology Clinic at South Egypt Cancer Institute with huge left cervical swelling. The condition started with left cervical swelling of insidious onset and progressive course so parent's sought medical advice and received medical treatment with no response then surgical removal of the swelling was done and histopathological examination revealed Castleman's disease hyaline vascular type and patient was put on follow up. At the age of 6years the child developed recurrent huge left cervical swelling not associated with trauma: fever: night sweating or itching. The child had no relevant family or past medical history. Examination of the child revealed good general condition with huge left cervical swelling occupying the upper and lower deep cervical regions about 6\*4 cm with lobulated surface firm to hard in consistency mobile in all directions with normal skin overlying and no other body swellings. Laboratory investigations were normal CT neck: chest and abdomen (Figure 3) revealed multiple well defined highly vascular matted lymph node masses seen in the left cervical region causing

compression and displacement of adjacent great neck vessels the largest one was 4\*2.7cm otherwise free. Complete Surgical removal of the cervical lymph nodes was done. Histopathological examination of excised lymph nodes revealed Castleman's diseases hyaline vascular type. Now patient is on regular follow up for 60months.



**Figure 3** CT neck showing multiple well defined highly vascular matted lymph node masses seen in the left cervical region causing compression and displacement of adjacent great neck vessels the largest one was 4\*2.7cm.

## Discussion

Lymphadenopathy may be localized affecting one anatomical region or generalized affecting 2 or more regions. In our case report we are presenting 2 cases of Lymphadenopathy. The first case is of generalized Lymphadenopathy with constitutional manifestations. There are large differential diagnoses of generalized Lymphadenopathy. It may result from different pathological processes as infections: autoimmune disorders: metabolic diseases and malignancy.<sup>10</sup> Certain drugs may cause generalized Lymphadenopathy as allopurinol: phenytoin: trimethoprim/sulfamethoxazole and penicillin. Several factors should be considered during establishing a differential diagnosis to Lymphadenopathy including patient age: site: size and consistency of enlarged lymph nodes and time course of Lymphadenopathy.<sup>1</sup>

Most of the cases of generalized Lymphadenopathy in children are infectious or benign in nature. In a case series of 628 patients undergoing nodal biopsy: benign or self-limited causes were found in 79 percent of patients younger than 30years of age: versus 59 percent in patients 31 to 50years of age and 39 percent in those older than 50years.<sup>11</sup> Patient was fully investigated to exclude infection: metabolic: autoimmune and malignant causes. Patient was finally diagnosed as multicentric hyaline vascular castleman's disease. Multicentric Castleman's disease is typically of the plasma cell type but in our case series the multicentric case is of hyaline vascular type.<sup>12</sup> Multicentric castleman's disease is characterized by generalized Lymphadenopathy: hepatosplenomegaly and usually associated with constitutional manifestations as fever: night sweating: severe fatigue: and anorexia. Patients may suffer from peripheral oedema: ascitis and pleural effusion. Patients usually have acute phase reaction with elevated ESR: CRP: fibrinogen and thrombocytosis: while hemoglobin and albumin levels are decreased.<sup>13</sup> Constitutional manifestations with elevated acute phase reactants in multicentric castleman's disease are due to excessive secretion of interleukin 6 which induces a pro- inflammatory syndrome with increase secretion of vascular endothelial growth factor (VEGF) which leads to increase angiogenesis and vascularization in the involved lymph nodes.<sup>14</sup> The second case report was a case of recurring localized



Lymphadenopathy. Localized Lymphadenopathy represents seventy five percent of all Lymphadenopathy: with more than 50% are seen in head and neck area.<sup>10</sup>

Infection is the most common cause of cervical Lymphadenopathy which is usually acute and self limited. While most cases are self limited: some causes such as atypical mycobacterium: toxoplasmosis: cat-scratch disease: sarcoidosis: and Kawasaki's syndrome may cause Lymphadenopathy for many months: and may be mistaken with malignancy.<sup>15</sup> Lymph node enlargement in the 2nd case was finally diagnosed as hyaline vascular castleman's disease. The second case was also presented in unusual very young age (2.5)years. Castleman's disease is a rare lymph proliferative disorder with an age range from 8years to 66years.<sup>12</sup>

Human immunodeficiency virus status is an important risk factor. Human immunodeficiency virus infected patients with multicentric castleman's disease have much frequent plasmacytic disease and the clinical course is less favorable than in non infected patients.<sup>16</sup> Multicentric castleman's disease especially in human immunodeficiency infected patients may be associated with malignancies as Kaposi sarcoma: B cell lymphoma: hodgkin's lymphoma and plasmacytoma. It may also be accompanied with POEMS syndrome (polyneuropathy: organomegaly: endocrinopathy: monoclonal gammopathy: skin changes).<sup>17</sup> Localized castleman's disease is treated by surgical excision which is curative in 90%-95% of cases. The prognosis is excellent with a 5years survival rate close to 100%.<sup>18</sup> In practice diverse treatments are used for multicentric castleman's disease: often in combination e.g.: surgery: corticosteroid and chemotherapy. Cyclophosphamide (750mg/m<sup>2</sup>) is given in monthly pulses. Vinblastin (8mg/m<sup>2</sup>/week) is also administered as authorized in the context of kaposi sarcoma. Monthly polychemotherapy is also an effective treatment regimen. In this context: the most effective combinations seem to be regimens like CHOP (cyclophosphamide: vincristine: doxorubicin: prednisolone) or ABVD (etoposide: ifosfamide: cisplatin alternating with doxorubicin: vinblastin: bleomycin and decarbazine). Anti-interleukin-6 antibody has also been successfully tried in the alleviation of systemic manifestations.<sup>19</sup> Other therapies include intravenous immunoglobulin: anti-herpes drugs e.g. acyclovir: ganciclovir in human immunodeficiency infected patients and human herpes virus positive disease: interferon alpha<sup>20</sup>: retinoic acid<sup>21</sup> and in intractable cases even autologous stem cell transplantation.

Castleman's disease is a rare cause of generalized Lymphadenopathy. Although: it's rare in children: it can occur at any age. Most of cases of multicentric Castleman's disease are plasma cell variant: yet hyaline vascular type may occur. Multicentric Castleman's disease can be successfully treated with monthly combination chemotherapy. Most cases of unicentric Castleman's disease are hyaline vascular type. Although: surgical removal of unicentric type is usually sufficient to achieve complete remission: recurrence can still occur.

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## Conflicts of interest

The authors declare there is no conflict of interests.

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