

## Case Reports

# Hyaline-vascular Variant Unicentric Castleman Disease with Paraneoplastic Pemphigus and Bronchiolitis Obliterans Treated with Rituximab: Case Report

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**Abstract** Castleman disease (CMD) is an uncommon lymphoproliferative disorder characterised by hyperplasia of lymphoid tissue. There are three histopathologic types of CMD: hyaline-vascular type, plasma cell type and mixed type. Hyaline-vascular CMD is typically unicentric, while plasma cell CMD tends to be multicentric. In rare occasion, CMD can be associated with paraneoplastic pemphigus (PNP), an autoimmune syndrome which encompasses a multitude of mucocutaneous and systemic clinical features. In children with PNP associated with Castleman disease, they have been reported to have very poor prognosis and high mortality rate as a result of respiratory compromise despite aggressive treatment. We report a case of unicentric, CD-20 positive, hyaline-vascular retroperitoneal CMD presenting with paraneoplastic pemphigus and bronchiolitis obliterans with significant clinical improvement in oral mucositis and the prevention of tumour recurrence, using regular rituximab (375 mg/m<sup>2</sup>/dose) and 3-day course of pulse methylprednisolone therapy (10 mg/kg/day) after tumour resection.

**Key words** Bronchiolitis obliterans; Castleman disease; Children; Paraneoplastic pemphigus; Rituximab

### Introduction

Castleman disease (CMD) was first described by Benjamin Castleman in 1954. It is an uncommon lymphoproliferative disorder characterised by hyperplasia of lymphoid tissue.<sup>1</sup> It is also known as angiofollicular lymphoid hyperplasia and giant lymph node hyperplasia, and it rarely involves the lung.<sup>2</sup> There are three histopathologic types: hyaline-vascular type (70%), plasma cell type (20%) and mixed type (10%). A broad spectrum

of clinical manifestations of CMD is described, ranging from an asymptomatic localised lymphadenopathy to a severe symptomatic generalised lymphadenopathy.<sup>3</sup> Clinical variants of CMD are commonly classified into unicentric and multicentric types, as proposed by McCarty et al in 1995.<sup>4</sup> Hyaline-vascular CMD is typically unicentric, while plasma cell CMD tends to be multicentric.<sup>5</sup> In rare occasion, CMD can be associated with paraneoplastic pemphigus (PNP), an autoimmune syndrome which encompasses a multitude of mucocutaneous and systemic clinical features.<sup>6</sup> In children with PNP associated with Castleman disease, they have been reported to have very poor prognosis and high mortality rate as a result of respiratory compromise despite aggressive treatment.<sup>7</sup>

We report a case of unicentric, CD-20 positive, hyaline-vascular retroperitoneal CMD presenting with paraneoplastic pemphigus and bronchiolitis obliterans with significant clinical improvement in oral mucositis and the prevention of tumour recurrence, using regular rituximab (375 mg/m<sup>2</sup>/dose) and 3-day course of pulse methylprednisolone therapy (10 mg/kg/day) after tumour resection.

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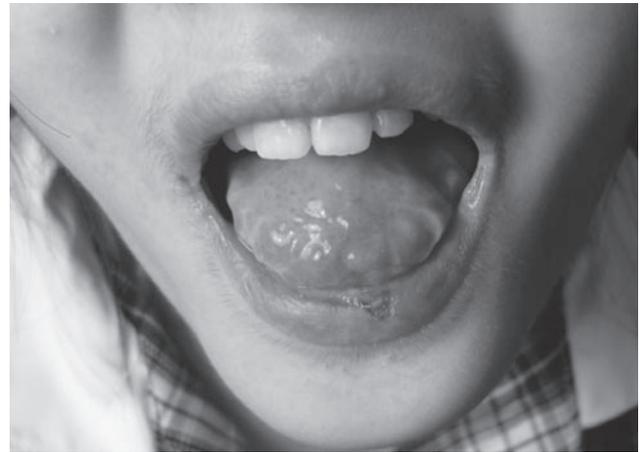
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## Case Report

A 17-year-old Chinese girl, with a past medical history of complete resection of an abdominal "benign lymphoid tumour" in mainland China at the age of two years and developed asthma-like symptoms since six years of age, was admitted to the paediatric intensive care unit of our hospital due to severe mycoplasma pneumonia complicated by right-sided pneumothorax in August 2006 at the age of 13 years. Physical examination during hospitalisation revealed bilateral basal crepitations over the chest. At that time, she received mechanical ventilatory support for a few days. After weaning off from mechanical ventilatory support, she remained oxygen dependent and was later discharged home with BiPAP. During out-patient clinic follow-up after discharge, she was noted to have painful mucositis with lichen planus like lesions affecting the tongue, mouth and lips (Figure 1), nail dystrophy and erythema of nail folds affecting all digits with no clubbing (Figure 2), and bilateral basal crepitations on chest auscultation. Other systems including cardiovascular, abdominal and neurological systems revealed no abnormalities. Chest radiograph showed bell-shaped, hyperinflated chest with prominent lung markings, especially in the basal regions (Figure 3). High resolution computed tomography of the chest showed hyperinflation with emphysematous and fibrotic changes in bilateral lungs, as well as bronchial dilatation and thickening with mosaic attenuation compatible with bronchiolitis obliterans and bronchiectasis (Figure 4). Electrocardiogram showed no evidence of right atrial or ventricular hypertrophy. Echocardiogram showed no evidence of pulmonary hypertension. Complete blood picture, erythrocyte sedimentation rate, C-reactive protein, liver and renal function tests were all normal. Antinuclear antibody, anti-glomerular basement membrane antibody, anti-skin antibody were all negative. Alpha-1 antitrypsin level was normal. Sweat test was negative. Immunoglobulin levels including IgA, IgG and IgM were all normal. Specific IgE against common aeroallergens were  $<0.35$  KU/L. Lymphocyte subset showed no major abnormality. Lung function test showed evidence of moderate to severe obstructive and restrictive impairment (Figure 5). Sleep study showed no evidence of obstructive sleep apnoea. The patient remained oxygen dependent requiring BiPAP at home since discharge from our hospital in August 2006. With gradual clinical improvement, she opted to stop the BiPAP therapy after nine months.

The patient had chronic cough all along, and the asthma-

like symptoms and chronic lung disease condition was treated with inhalational corticosteroid (fluticasone 125 microgram twice daily), long acting beta-agonist and nocturnal oxygen therapy during sleeping time. However, there was gradual deterioration in 2008 and she resumed BiPAP during sleep time as well as portable oxygen therapy during exertion as needed. Polysomnography was performed



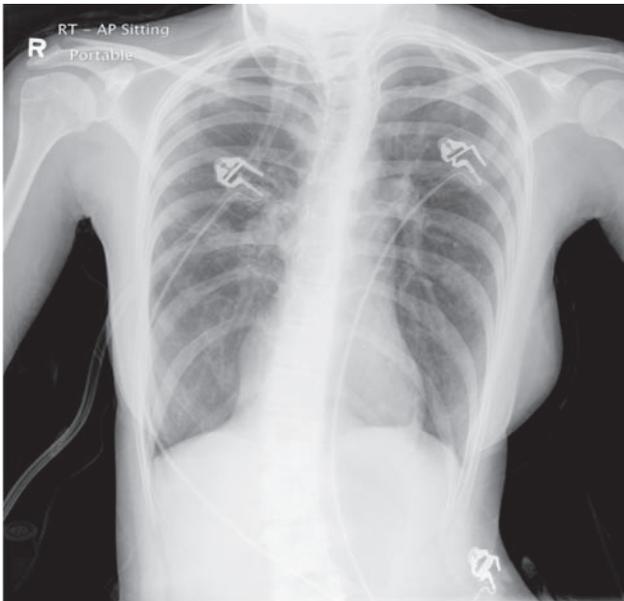
**Figure 1** Painful mucositis with lichen planus like lesions affecting tongue, mouth and lips.



**Figure 2** Nail dystrophy and erythema of nail folds affecting all digits of hands and feet.

showing evidence of nocturnal hypoventilation and nocturnal hypoxemia, with no obstructive or central apnoea. In November 2008, a six centimeter palpable non-tender lower abdominal mass was incidentally detected during follow-up. There were no associated symptoms such as abdominal distension, abdominal pain, vomiting, and weight loss. Abdominal and pelvic computed tomography showed a large homogeneous, well-circumscribed and contrast-

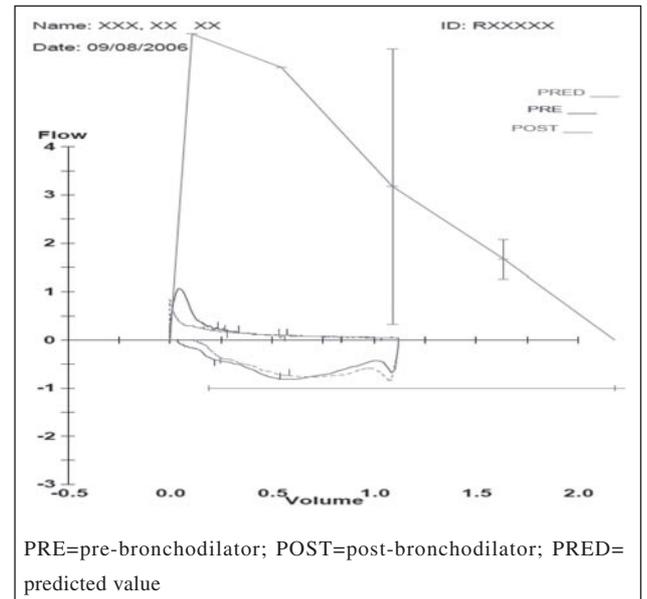
enhancing left retroperitoneal mass measured 8.5 cm x 7.2 cm x 8.3 cm extending from lower L4 level down to S1 level compatible with a primary retroperitoneal tumour (Figure 6). Tumour markers including alpha-fetoprotein, carcinoembryonic antigen, and human chorionic gonadotrophin were all normal. She underwent total surgical resection of the retroperitoneal mass. Pathological examination of the resected mass revealed an oval-shaped pinkish soft tissue mass weighed 170 grams and measured 8.5 cm x 7.5 cm x 6 cm. The outer surface was smooth with



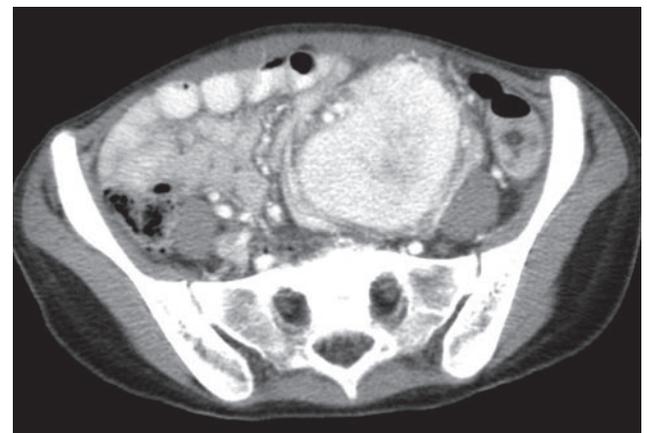
**Figure 3** Chest radiograph showed bell-shaped, hyperinflated chest with prominent lung markings, especially in the basal regions.



**Figure 4** High resolution computed tomography of the chest showed hyperinflation with emphysematous and fibrotic changes in bilateral lungs, as well as bronchial dilatation and thickening with mosaic attenuation compatible with bronchiolitis obliterans and bronchiectasis.



**Figure 5** Lung function test showed evidence of moderate to severe obstructive and restrictive impairment.



**Figure 6** Abdominal and pelvic computed tomography showed a large homogeneous, well-circumscribed and contrast-enhancing retroperitoneal mass measured 8.5 cm x 7.2 cm x 8.3 cm.

slightly lobulated contour, covered by small amount of fatty tissue and whitish thin capsule. Cut surface of the mass showed pinkish homogeneous appearance, with firm consistency and delicate fibrous septa inside the mass. Sections of the retroperitoneal mass showed a lymph node with intact capsule and largely obliterated sinuses. Multiple regressed follicles were present, each surrounded by a prominent mantle zone. Many of the follicles exhibited lymphoid-depleted germinal centres traversed by vessels. Hyalinized fibrous septa were present. Immunohistochemical staining for CD21 demonstrated follicular dendritic cell network with accentuation in the follicle centers. There was no evidence of transformation to a follicular dendritic cell tumour or malignant lymphoma. Immunohistochemical staining showed that the reactive B lymphocytes in the lymph node were positive for CD20 and negative for human herpesvirus-8. The overall features were consistent with Castleman disease of hyaline-vascular type, with no evidence of malignancy. Gallium scan was performed and showed static whole body study with no evidence of multicentric form of Castleman disease.

The patient was well after discharge from the hospital after the surgery. However, she developed increased respiratory distress again at three months after tumour resection. Computed tomography was repeated two months after surgery, showing recurrence of retroperitoneal tumour measured 1.3 cm x 0.9 cm x 5.7 cm in left para-aortic region which did not respond to intravenous immunoglobulin (IVIG) therapy and oral steroid. Regular pulse methylprednisolone and rituximab therapy were subsequently started since three months after surgery with significant clinical improvement in oral mucositis. A 3-day course of pulse methylprednisolone (10 mg/kg/day) was given monthly for one year. Rituximab 375 mg/m<sup>2</sup> (or 500 mg) was initially given weekly for four doses and biweekly for four doses, followed by monthly and later bimonthly regimen, tailing off in two years. After starting rituximab therapy for three months, follow-up CT abdomen showed a small resolving left retroperitoneal lesion. Latest contrast CT abdomen in July 2010, after 14 months rituximab therapy, showed no more recurrence of retroperitoneal tumour. However, high resolution CT thorax showed progression of bronchiectasis at both lungs with mild mosaic perfusion pattern remained. The patient is currently waiting for receiving lung transplant surgery.

## Discussion

Castleman disease, also known as angiofollicular

lymphoid hyperplasia, is an uncommon lymphoproliferative disorder which was first described by Benjamin Castleman in 1954.<sup>1</sup> The various types of Castleman disease are characterised by distinctive lymphoid architectural changes in all nodal compartments. There are three histopathologic types: hyaline-vascular type (70%), plasma cell type (20%) and mixed type (10%). Hyaline-vascular CMD is characterised by lymphoid follicular hyperplasia with involuted germinal centres, replaced partly or totally by deposit of hyaline material and transfixed by a radially penetrating vessel.<sup>8</sup> On the other hand, plasma cell CMD is characterised by follicular hyperplasia of hyperplastic germinal centres in which the interfollicular areas are occupied by large sheets of plasma cells.<sup>9</sup> The clinical variants of CMD are commonly classified into unicentric and multicentric types, as proposed by McCarty et al in 1995.<sup>4</sup> In unicentric hyaline-vascular CMD, a single or chain of lymph nodes is involved in various regions such as the thorax (63%), abdomen (11%), and axilla (4%). Other extrathoracic sites, including the neck, orbit, pelvis, and retroperitoneum, have also been reported.<sup>8,10-15</sup> Patients may be asymptomatic or develop symptoms caused by local mass effects, while systemic symptoms are uncommon.<sup>16</sup> In the unicentric plasma cell type, constitutional symptoms and laboratory abnormalities are more commonly found in addition to lymph nodes enlargement.<sup>17</sup> On the other hand, patients with multicentric CMD have multifocal lymphadenopathy. They usually develop systemic symptoms, including fever, night sweats, fatigue, anorexia, weight loss. They may develop hepatosplenomegaly, edema, ascities, pleural or pericardial effusions, skin rash and seizure. Laboratory abnormalities are commonly found in multicentric CMD, such as anemia of chronic disease or hemolysis, thrombocytopenia, elevated erythrocyte sedimentation rate, hypoalbuminuria, abnormal liver function test and polyclonal increase in immunoglobulins.<sup>18</sup> It has been found that excessive production of interleukin-6 (IL-6) is implicated in many of these manifestations of CMD.

Treatment of CMD depends on the type of the disease. For unicentric CMD, surgery is the mainstay of treatment and is usually curative, whether of the hyaline-vascular or plasma cell variant.<sup>19</sup> When surgery is not an option, irradiation is an effective alternative with response rates up to 72%.<sup>20</sup> On the other hand, symptomatic patients with multicentric CMD require systemic therapy with several available options. Glucocorticosteroid such as prednisolone is often used as a temporary intervention in acute situations to quickly ameliorate symptoms and partially improve

lymphadenopathy. Symptoms are however likely to recur after discontinuing the treatment. Based on the lymphoproliferative process in CMD, a variety of chemotherapy used in the treatment of non-Hodgkin's lymphoma have been utilised in the treatment of CMD, depending on the "aggressiveness" of the disease. Chlorambucil, cyclophosphamide, vinblastine, etoposide and interferon have been effective in some patients.<sup>18, 21-24</sup> Combination chemotherapy regimen such as CVP (cyclophosphamide, vincristine and prednisolone) or CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) have significant activity.<sup>18,19,21</sup>

Rituximab, a monoclonal antibody to CD20, can be considered in CD20-positive multicentric CMD, and it has been effective in both HIV positive or negative patients. Three out of five HIV-positive patients in one series were reported to achieve complete remission for 4-14 months with rituximab.<sup>25</sup> In another case series, two out of three HIV-negative patients achieved near complete remission for 16-40 months with rituximab.<sup>26</sup> Based on the association between IL-6 overproduction and multicentric CMD, the use of a humanised monoclonal antibody to the human IL-6 receptor (tocilizumab) can be considered.<sup>27</sup>

Paraneoplastic pemphigus (PNP), first described in 1990, is an autoimmune syndrome which encompasses a multitude of mucocutaneous and systemic clinical features.<sup>6</sup> Mucocutaneous involvement is prominent, with painful erosive lesions involving the oral, nasal, upper gastrointestinal, respiratory, ocular and genital epithelium.<sup>28</sup> In our case, there was prominent mucocutaneous involvement of the oral cavity with lichen planus like lesions affecting the tongue, mouth and lips. Cutaneous manifestations often contain polymorphous inflammatory macules, papules, and plaques. Histopathologic features include acantholysis, intraepidermal blister formation, immunoreactant deposition along the basement membrane and within epithelial intercellular spaces.<sup>7</sup> Although the immunopathological findings vary, the presence of antiplakin protein autoantibodies is found to be a constant feature. PNP is mostly associated with specific B-cell lymphoproliferative neoplasms: non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and Castleman disease, and less commonly thymoma and sarcoma.<sup>29</sup> PNP is rarely seen in children. Mimouni et al reported that Castleman disease was the most common underlying neoplasm associated with PNP in childhood, occurring in 12 out of 14 children in the case series.<sup>30</sup> In another case series report, Wang et al commented that Castleman disease associated with PNP was a commonly reported subtype of PNP in China.<sup>31</sup> It

was demonstrated that the use of IVIG infusion peri-operatively could prevent the deterioration in lung function. It is therefore important for clinicians to look for the underlying Castleman disease in children as prompted by the combination of PNP and bronchiolitis obliterans. And the early diagnosis of Castleman disease by imaging may detect the lesion that could be resected and thus prevent further progression of the bronchiolitis obliterans which is an immune mediated complications related to the Castleman disease. Unfortunately, PNP associated with CMD has a very poor prognosis and a high mortality rate due to the established lung damage. It has been postulated that severe respiratory compromise results from IgG deposits in the epithelium of the bronchi, as well as pulmonary epithelial acantholysis and intraepithelial cleavage.<sup>7</sup> The severe respiratory compromise was seen in our case with gradual development of oxygen dependence and the requirement of nocturnal BiPAP. Majority died of respiratory failure. No therapy has been reported to be consistently effective.<sup>7</sup> Surgical removal of the underlying neoplasm is not usually curative. Various treatment options such as corticosteroid, cyclosporine, cyclophosphamide, azathioprine, gold, dapsone, thalidomide, mycophenolate mofetil, rituximab, intravenous immunoglobulin have been generally unsuccessful.<sup>32-35</sup> In our case, the patient developed increased respiratory distress again at 3 months after surgery, with recurrence of tumour refractory to IVIG and oral steroid. Regular rituximab and pulse methylprednisolone therapy in our patient on the other hand led to significant clinical improvement in oral mucocutaneous lesions. The residual retroperitoneal tumour nearly completely resolved after one-year treatment of regular rituximab and pulse methylprednisolone therapy. To our knowledge, unicentric CMD presenting as paraneoplastic pemphigus with bronchiolitis obliterans responding dramatically to regular rituximab and pulse methylprednisolone therapy post-operatively has not been reported in the literature previously.

## Conclusion

We report a case of unicentric, CD-20 positive, hyaline-vascular retroperitoneal CMD presenting with paraneoplastic pemphigus and bronchiolitis obliterans with significant clinical improvement in oral mucositis and the prevention of tumour recurrence, using regular rituximab (375 mg/m<sup>2</sup> /dose) and 3-day course of pulse methylprednisolone therapy (10 mg/kg/day) after tumour resection.

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