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Castleman's Disease of the Neck: Report of Four Cases with Unusual Presentations

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Abstract

Purpose—Most of the previously reported cases of Castleman's disease (CD) in the neck were of the hyaline vascular type and the most common sign was an asymptomatic neck mass. To achieve a more general recognition of CD in the neck, we present four cases of CD in the neck with unusual presentations.

Patients and Methods—We describe four cases of CD in the neck with unusual clinical manifestations, different histopathologic subtypes and discuss the problems arising in their clinical findings.

Results—Two cases were plasma cell type with multiple bilateral enlarged lymph nodes and systemic manifestations. Two cases presented as a solitary mass were hyaline vascular type. One case underwent twice local recurrence and evolved from the hyaline vascular CD to follicular dendritic cell sarcoma.

Conclusions—Cervical plasma cell CD may have a tendency to present as multiple masses on the both sides with systemic manifestations. It is necessary to pay more attention on the overgrowth of follicular dendritic cells in the hyaline vascular CD, which might represent a precursor of follicular dendritic cell sarcoma.

Keywords

Castleman's disease; Neck; POEMS syndrome; Follicular dendritic cell sarcoma; Clinical manifestation

In 1956, Castleman and colleagues first described the clinicopathologic entity of mediastinal lymphoid hyperplasia with hyalinization of follicles and interfollicular vascular formation.¹ Subsequent reports described additional sites of disease and different names were used for this entity, including Castleman's disease (CD), angiofollicular or giant lymph node hyperplasia.² CD represents a morphologically distinct form of lymph node hyperplasia rather than a neoplasm or hamartoma. The etiology and pathogenesis of CD are not

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completely understood. Microscopically, two major categories have been described.³ The first, designated as hyaline vascular type shows large follicles scattered in a mass of lymphoid tissue. The follicles show marked vascular proliferation and hyalinization of their abnormal germinal centers. Many of large cells with vesicular nuclei present in the hyaline center are follicular dendritic cells. There is a tight concentric layering of lymphocytes at the periphery of the follicles (corresponding to the mantle zone), resulting in an onion-skin appearance. The second major morphologic category of CD is known as the plasma cell type. It is characterized by a diffuse plasma cell proliferation in the interfollicular tissue. The hyaline vascular changes in the follicles are inconspicuous or absent. CD is clinically heterogeneous with either solitary CD (SCD) or multicentric CD (MCD). Over 90% of the cases are of the hyaline vascular type, and the remainder are of the plasma cell type.³ The former usually presents with asymptomatic solitary mass and can mostly be treated effectively with surgery,^{4–6} whereas the plasma cell type often has a more aggressive course and tends to be MCD with systemic symptoms (including fever, night sweats, weight loss, and recurring infections) and multiple peripheral lymphadenopathies.^{7, 8} CD with severe systemic manifestations and poor prognosis is frequently associated with POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin changes), renal or pulmonary complications and malignancies, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and follicular dendritic cell sarcoma.^{8–13}

CD may occur anywhere along the lymphatic chain, but the mediastinum is the most common location. Neck involvement with CD is relatively uncommon. To our knowledge, most descriptions of CD in the neck were isolated cases or small series and most of the previously reported cases of CD of the neck were of the hyaline vascular type.^{4–6}

In this article, we describe four cases of CD in the neck with unusual presentations, different histopathologic subtypes and discuss the problems arising in their clinical findings.

Reports of Cases

CASE 1

In July, 2004, a 50-year-old man was admitted because of bilateral cervical masses, erectile failure, and burning pain, numbness, and weakness of the four extremities. His symptoms started eight years earlier when he initially noticed painless slowly enlarging masses in the both sides of his neck, but he did not pay any attention. He noticed erectile failure in July 2003. In early 2004 he developed progressive leg weakness, burning sensations and tenderness in the feet, and numbness below the knees. By mid 2004 numbness developed in the finger tips followed by progressive weakness of the hands. Around that time, he became aware that his skin was turning dark. He also complained of night sweats and weight loss. His strength continued to deteriorate and he could no longer walk or hold a pen.

His physical examination was remarkable for neck multiple swelling lymph nodes on the both sides (Fig 1). They were nontender and mobile. Muscle atrophy over legs and edema of both feet were also observed. His skin on face and neck was hyperpigmentation. He had difficulty in standing unassisted. His stance was wide-based and his gait demonstrated a bilateral foot drop. Contrast-enhanced axial CT scan showed many well-margined, intensely enhancing masses in the both sides of the neck. Abdominal ultrasonography revealed splenomegaly. The laboratory examination was normal except a monoclonal peak was seen in the gamma region on serum protein electrophoresis, identified by immunoelectrophoresis as lambda light chains (M protein positive). Serological screening for human immunodeficiency viruses (HIV) was negative.

The patient was first diagnosed with POEMS syndrome due to the characteristic clinical findings. These included lymphadenopathy, polyneuropathy, splenomegaly, erectile failure, M protein positive and skin lesions. He was initially treated with oral melphelan 6 mg daily for 7 days, accompanied by prednisolone 60 mg daily for 14 days. However, there was no symptomatic relief. A bilateral functional neck dissection was performed in August 2004. Histological examination of bilateral cervical lymph nodes revealed numerous lymphoid follicles with small germinal centers surrounded by small lymphocytes and the interfollicular tissue with increased populations of plasma cells (Fig 2). The clinical manifestations and the histological findings were compatible with the plasma cell type of MCD with features of POEMS syndrome. The postoperative clinical course was uneventful and the patient clinically improved with alleviation of burning pain, numbness, weakness of the four extremities. A CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) combination chemotherapy regimen was discussed with the patient, but he did not accept. This patient was discharged to home with instructions for further out-patient follow-up with us. Unfortunately, the follow-up was lost after discharge.

CASE 2

In January 2007, a 57-year-old man presented to our department with a 2-month history of a mass in the left side of his neck which had rapidly increased in size. The patient underwent a fine needle biopsy (FNB) of the left cervical lymph node one month earlier in another hospital. The FNB result was subsequently reported as “negative for malignant cells”.

Clinical examination was remarkable for the left cervical lymphadenopathy measuring 12×8 cm. The lymphadenectasis were also found on the right side of the neck. A magnetic resonance (MR) scan examination for the cervical masses revealed isointense signals on T₁-weighted images and characterized of both low as well as high signals on T₂-weighted images. Abdominal ultrasonography revealed splenomegaly. Routine laboratory data were normal. There was no serological indication of active HIV infection. These findings were thought most likely to represent malignant lymphoma.

Subsequently, a left cervical lymph node biopsy was performed. Sections showed concentrically arranged mantle zone lymphocytes surrounding germinal centers. It also revealed moderate to large sheets of mature plasma cells in the interfollicular area (Fig 3). Taken together, these findings were consistent with the plasma cell type of MCD. Accordingly the patient was started on a CHOP combination chemotherapy regimen. The patient appeared to tolerate this well, achieving some resolution of swelling lymph nodes. This patient was discharged to home on day 3 following the first course of chemotherapy. Unfortunately, he failed to keep his chemotherapy appointment. Six month later the patient returned to the emergency department with dyspnoea. On examination he was extremely ill, febrile having a respiratory rate of 40 per minute, and diffuse crepitations throughout both lung fields and an oxygen saturation of 60% on room air. Chest radiology revealed widespread reticular pattern with hilar and paratracheal nodal enlargement. He had to be artificially ventilated because of severe respiratory failure and died in July 2007. Permission for autopsy was not obtained.

CASE 3

In June 1996, a 36-year-old woman complained of a painless mass on the left side of the neck for 2 years. During the previous 1 year her left adrenal cortex had been affected by adenocarcinoma. She underwent a left nephrectomy and received a total of four courses of chemotherapy (paclitaxel, doxorubicin, cyclophosphamide) postoperatively.

On physical examination, a large, discrete, mobile, non-tender mass of 5×6 cm in dimension was found in the left supraclavicular region. The clinical findings prompted a diagnosis of cervical lymph node metastasis of adenocarcinoma. Excision biopsy of the left supraclavicular mass was performed. The removed mass consisted of lymphoid tissue with follicles containing multiple capillaries surrounded by hyaline sheaths. Vascular proliferation with hyaline change were prominent at the periphery of the follicles, which were surrounded by concentric cuffs of lymphocytes arranged in an onion skin pattern (Fig 4). The changes were consistent with the diagnosis of the hyaline vascular type of CD.

In July 1997, the patient presented with recurrent left neck mass. We removed the mass together with peripheral soft tissue. The resected recurrent lesions demonstrated histopathologic features identical to those seen in the initial biopsy specimen. In early 1998, the patient presented again with an enlarged mass in her left neck. Her symptoms were similar to those in 1997. Excision of the neck mass was performed and histopathological evaluation revealed changes consistent with the hyaline vascular type of CD. However, there were areas in which the follicular dendritic cells proliferated beyond the boundaries of the original follicles, forming multiple irregular, small, pale-staining islands in the interfollicular zones (Fig 5). She was admitted again in March 1999 because of a swelling lymphadenopathy in her left neck. Left radical neck dissection was performed. Microscopically, the mass was composed mostly of spindly cells arranged in a storiform pattern and sprinkled with small lymphocytes, the follicular dendritic cells had indistinct cell borders, lightly eosinophilic cytoplasm, and round vesicular nuclei, some binucleated cells and mitotic figures were seen (Fig 6). The tumor cells were positive for the follicular dendritic cell markers CD21 (Fig 7), CD35, CD23 and epithelial membrane antigen. The findings of histopathological evaluation and immunohistochemical examination were consistent with a diagnosis of follicular dendritic cell sarcoma. She died of pulmonary metastases 11 months later.

CASE 4

In June 2000, a 46-year-old woman complained of a painless lump on the left side of the neck for the duration of 3 years, which had slowly increased in size. On physical examination a discrete, mobile, non-tender mass of 1.8×2 cm in dimension was found behind the angle of the jaw on the left side. CT scan showed a 2 cm homogeneously enhancing mass with well-circumscribed margin below the left parotid gland. The remainder of the physical examination was unremarkable. FNB was subsequently done, raising the possibility of Warthin's tumor. The patient underwent a left superficial parotidectomy. Histopathological evaluation revealed lymphoid hyperplasia with an increased number of germinal centers that showed marked vascular proliferation and hyalinization. It also revealed marked vascular proliferation with hyaline change in the interfollicular area (Fig 8). These findings were consistent with the hyaline vascular type of CD. Postoperative recovery was uneventful and the patient has been free of disease for nine years.

Discussion

Most of the previously reported cases of CD of the neck were of the hyaline vascular type and these usually present as a solitary mass lesion both on clinical examination and on imaging.^{4–6} This was also the observation in our case, as the patients in case 3 and 4 presented with solitary mass were both of the hyaline vascular type. The exception was in the case 1 and 2 where the patient presented as multiple bilateral lymphadenopathies with generalized symptoms and the histology was of the plasma cell type. It may be that the plasma cell type of CD of the neck has a greater tendency to present as multiple rather than solitary neck masses.

It is now increasingly clear that there are different etiologies for each of these different subtypes. MCD is related to abnormal immune response and viral infection. A high level of cytokine interleukin 6 (IL-6) has been reported in patients with MCD and has been implicated in the pathogenesis of the disease.^{10, 14} The level has shown to return to normal after removal of the lymph node masses, suggesting that the source of IL-6 had been removed.¹⁴ Additionally, treatment with the monoclonal anti-IL-6 antibody and thalidomide (a disruptor of the IL-6 pathway) have shown to alleviate symptoms of MCD, further implicating that IL-6 may play an important role in the pathogenesis of MCD.^{15–17} Regarding the latter, a definite link has been documented between human herpesvirus 8 (HHV-8, or Kaposi's sarcoma-associated herpesvirus) and a subset MCD.^{8, 18–20} HHV-8 infection is present in nearly 100% of MCD cases associated with HIV-1 infection, and in about 50% of cases that are HIV-1 negative.^{21, 22} Clinically, HHV8-positive MCD is more aggressive, and has a poor prognosis with a median survival of less than 30 months.^{12, 22} The most common causes of death are sepsis, followed by malignancies.^{11, 18} HHV-8 is known to encode a viral-IL6, which can induce production of endogenous human IL-6.²³ Overproduction of the cytokine IL-6, either native or virally encoded, has been hypothesized to drive plasma cell proliferation and can explain the systemic manifestations in patients with the plasma cell type of CD.^{16–19} It is suggested that HHV-8 infection may initiate aberrant IL-6 activity causing both Castleman's lymphoproliferation and the plasma cell dyscrasia of POEMS syndrome.¹⁹ Our first case's clinical manifestations were consistent with the diagnostic criteria for POEMS syndrome. The patient clinically improved with alleviation of constitutional symptoms after bilateral functional neck dissection. Our second case presented here was characterized by bilateral cervical lymphadenopathy, splenomegaly and died of severe pulmonary infection within 8 months. The clinical findings and courses of our cases (case 1 and case 2) provide indirect evidence (these included POEMS syndrome, clinically improved with alleviation of symptoms after removal of the lymph node masses, and died of severe pulmonary complication within 8 months) in support of the above information and hypotheses. Unfortunately, HHV-8 viral load and IL-6 levels were not checked in our cases.

The pathogenesis of the hyaline vascular type of CD is currently unknown. An important theme of the hyaline vascular type of CD is the active participation in it of a variety of nonlymphoid cellular components. One such component is the follicular dendritic cell, which is prominently present in the hyalinized nodules that characterize the disease and which is thought by some authors to be the core of the pathogenesis of this disorder. These cells can become atypical (dysplastic) both in the abnormal germinal centers and in the intervening tissue, and can manifest cytogenetic and molecular evidence of clonality. Furthermore, they may result in the formation of fullblown follicular dendritic tumors.³ Neoplasms showing follicular dendritic cell differentiation were first recognized by Monda et al. in 1986.²⁴ The natural history of follicular dendritic cell sarcoma is variable and often difficult to predict. Although follicular dendritic cell sarcoma has traditionally been viewed as an indolent tumor with a tendency toward local recurrence but a low risk of metastasis, the tumor is sometimes highly aggressive, causing death within 2 years.¹³ Approximately 15% of the reported cases of follicular dendritic cell sarcomas show an association with CD, in that both components are identified histologically at presentation, or the latter develops at the same site of a previously diagnosed hyaline-vascular CD.^{13, 25} Chan et al analysed 17 cases with follicular dendritic cell sarcoma. In their series, the diagnosis of the hyaline vascular type of CD was made simultaneously with follicular dendritic cell sarcoma in 1 patient, and 5.5 years earlier in the other.¹³ The evolution from hyaline vascular CD to follicular dendritic cell sarcoma appears to pass through a phase of extrafollicular overgrowth of follicular dendritic cell that lack significant cellular atypia.¹³ In our case 3, follicular dendritic cells overgrowth also could be identified in the interfollicular zones and the hyaline vascular type of CD preceded the development of follicular dendritic cell

sarcoma at the same anatomic site by 3 years. Although the hyaline vascular type of CD by definition present as a single mass, microscopic changes suggesting an early stage of the same process are sometimes seen in adjacent nodes.³ This gives a possible reason for the twice local recurrence after excision noted in our case 3.

CD must be included in the differential diagnosis of cervical nodal enlargements. The diagnostic problem is because it can be confused with other neoplasms of the head and neck. The primary diagnosis of CD is extremely difficult. Preoperative work up such as FNB and imaging study is of limited value. Case initially diagnosed as Warthin's tumor by FNB has been reported in the parotid gland.²⁶ Similar misdiagnosis was also occurred in one of our patients. We initially made tentative diagnoses of POEMS syndrome (case 1), malignant lymphoma (case 2), cervical lymph node metastasis of adenocarcinoma (case 3), and Warthin's tumor (case 4) respectively, before histopathologic examination was performed. The histopathologic evaluation is the only way to make a final diagnosis. Surgical resection is the primary treatment for the hyaline vascular type of CD in the head and neck and is curative in virtually all cases.^{4, 5} The plasma cell type is frequently associated with systemic manifestations and is often refractory to systemic therapy with corticosteroid and chemotherapy, particularly in the multicentric form. At present, there is no consensus as to the optimal management strategy for MCD. Different treatment options have been described in the literature that usually involves chemotherapy,^{8, 12} radiotherapy,¹² immune modulators,^{16, 17} anti-IL-6 monoclonal antibodies.¹⁵

In this report, 4 cases of CD in the neck are presented. CD should be considered in the differential diagnosis of cervical nodal enlargements. The plasma cell type of CD in the neck may have a tendency to present as multiple masses on the both sides with systemic manifestations. Definitive diagnosis rests on histopathologic evaluation of the excised specimen. It is necessary to pay more attention on the overgrowth of follicular dendritic cells in the hyaline vascular type of CD, which might represent a precursor of follicular dendritic cell sarcoma.

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Figure 1.
Photograph reveals of multiple swelling cervical lymph nodes on the both sides (case 1).

Figure 2. Photomicrograph of the plasma cell type of CD (case 1). In the left field, a germinal center is surrounded by a concentric arrangement of small lymphocytes. The interfollicular area contains aggregates of mature plasma cells and some small vessels. (hematoxylin-eosin stain, original magnification $\times 200$)

Figure 3.

Photomicrograph of the plasma cell type of CD (case 2). It shows concentrically arranged mantle zone lymphocytes surrounding two germinal centers (upper field). The interfollicular region shows a massive infiltration by plasma cells and some small vessels. (hematoxylin-eosin stain, original magnification $\times 200$)

Figure 4. Photomicrograph of the hyaline vascular type of CD (case 3). It shows concentric layering of small lymphocytes around a germinal center. The pale follicle contains many follicular dendritic cells with vesicular nuclei and some hyalinized vessels. Hyalinized vessels are also prominent at the periphery of the follicle. (hematoxylin-eosin stain, original magnification $\times 200$)

Figure 5.

The hyaline vascular type of CD with follicular dendritic cell overgrowth (Case 3). In the interfollicular region, there are irregular lightly eosinophilic patches representing overgrowth of follicular dendritic cells with ovoid vesicular nuclei. There is no significant cellular atypia, and these cellular clusters do not exhibit destructive growth. This lesion subsequently recurred as a frank follicular dendritic cell sarcoma (see Fig. 6). (hematoxylin-eosin stain, original magnification $\times 200$)

Figure 6. Photomicrograph of follicular dendritic cell sarcoma (case 3). The tumor is composed mostly of spindly cells arranged in a storiform pattern and sprinkled with small lymphocytes, some binucleated cells and mitotic figures are seen. (hematoxylin-eosin stain, original magnification $\times 200$)

Figure 7. Immunohistochemical staining of follicular dendritic cell sarcoma is shown (case 3). The tumor cells show intense staining with CD21 antibody. A focal network of tumor cells is well highlighted. (original magnification×200)

Figure 8. Photomicrograph of the hyaline vascular type of CD (case 4). A hyaline vascular follicle is shown. The mantle lymphocytes lie in a concentric ring around the reactive germinal centre. It also reveals conspicuous vascular proliferation with hyaline change in the interfollicular region. (hematoxylin-eosin stain, original magnification $\times 200$)