Castleman's disease is a rare lymphoproliferative disorder that is easily misdiagnosed. When it occurs in the head/neck and thorax, it can pose a diagnostic dilemma because of its lack of any specific presenting characteristics and distinguishing radiographic features. An accurate histopathologic diagnosis and careful staging are crucial to planning treatment. The highly vascular nature of the tumor makes surgical management challenging, and it warrants preoperative embolization whenever possible. We report 3 cases of Castleman’s disease that involved the head/neck and thorax. We also review the presenting clinical features of Castleman’s disease, its histopathologic characteristics, and the diagnostic and treatment challenges that it poses.

Introduction

Castleman’s disease is a rare lymphoproliferative disorder that presents with or without constitutional symptoms. Many terms have been used over the years to describe this entity, including giant lymph node hyperplasia, angiomatous lymphoid hamartoma, benign giant lymphoma, and follicular lymphoreticuloma.

The entity was first described in 1956 by Castleman et al as a benign, localized enlargement of hyperplastic lymph nodes.1 In 1970, Flendrig reported that this disorder has two separate histologic features.2 Based on these features, Keller et al in 1972 subclassified Castleman’s disease into two types: hyaline-vascular and plasma-cell.3 In addition, some patients have a mixed variant.

Clinically, Castleman’s disease can be either localized or multicentric. The localized form is more common:

- Approximately 90% of cases of the localized form are of the hyaline-vascular type. Patients present with a solitary mass, and their disease typically follows a benign course.4
- Most cases of the multicentric form are of the plasma-cell type. Patients present with a systemic illness that manifests as disseminated lymph nodes, constitutional symptoms (e.g., fatigue, fever, weight loss, and sweats), autoimmune abnormalities, recurrent infections, and laboratory abnormalities (e.g., anemia, hypoalbuminemia, hypergammaglobulinemia, and an increased erythrocyte sedimentation rate). The multicentric form is aggressive and often culminates in death secondary to infectious complications or malignancy (e.g., lymphoma, Kaposi’s sarcoma, or follicular dendritic cell sarcoma); malignancies have been reported to arise in as many as 32% of patients with multicentric Castleman’s disease.3-5

Both the hyaline-vascular and plasma-cell types of Castleman’s disease are usually accompanied by a systemic inflammatory response. The clinical course may also be complicated by acquired systemic amyloidosis. Following tumor resection, amyloid deposits and systemic inflammation regress.6

Multicentric Castleman’s disease in the absence of human immunodeficiency virus (HIV) infection is associated with non-Hodgkin’s lymphoma. Hodgkin’s disease may occur with the localized form of the plasma-cell type of Castleman’s disease, usually in the same region.7 In HIV-positive patients, multicentric Castleman’s disease is associated with human herpesvirus type 8 (HHV8), which is a Kaposi’s-sarcoma–associated herpesvirus. In one study, the incidence of Kaposi’s-sarcoma–associated, HHV8-related non-Hodgkin’s lymphoma in a cohort of HIV-positive patients with multicentric Castleman’s disease was 15-fold higher than the incidence in the general HIV-positive population.8

The most common location of Castleman’s disease is the thorax; the neck is the second most common site, although only about 70 such cases have been reported (table 1).9 The disease appears to have a predilection for men, and it usually occurs in the third through fifth decades of life (the youngest reported patient was diagnosed at 6 weeks...
of age). The incidence of Castleman’s disease is low in the pediatric population; when it does occur, these patients appear to have a more favorable outcome than do adults.

Collectively, we were involved in the treatment of 3 patients with Castleman’s disease. Patients 1 and 2 were treated at Wilford Hall Medical Center in San Antonio, Texas, by two of the authors (J.L.N. and J.B.), and patient 3 was treated at The Johns Hopkins Hospital in Baltimore by the third author (M.C.). All 3 patients had the localized form and the hyaline-vascular type of Castleman’s disease as determined by surgical lymph node biopsy. Follow-ups were conducted by clinic visits and telephone interviews. In this article, we describe these 3 cases, and we review the entire course of Castleman’s disease, including its clinical features at presentation, its histopathologic characteristics, and the diagnostic and treatment challenges it poses.

Case reports

Patient 1. A 58-year-old woman presented with a 5-year history of a persistent, enlarging left lateral neck mass. Because she had previously undergone multiple excisions of benign neuromas in her neck, we suspected that this mass represented another recurrence. The patient also complained of right-sided neck numbness and tingling. The remainder of her medical history was unremarkable.

On magnetic resonance imaging (MRI), the mass measured 5.2 × 3.3 cm. No impingement of the esophagus or trachea was noted. Fine-needle aspiration cytology identified atypical mesenchymal-type cells in a background of lymphoid tissue, represented by a mixture of T and B cells, with the former predominating. Negative flow-cytometry results and the nonspecific nature of the cytologic findings did not permit a diagnosis of lymphoma.

The patient was taken to the operating room for excisional biopsy under general anesthesia. The subplatysmal mass was found to be adherent to the clavicle. Final pathology revealed the hyaline-vascular type of localized Castleman’s disease. The patient was referred for radiation therapy because of concerns about possible positive margins after excisional biopsy. At the 18-month follow-up, she had not experienced any complication or recurrence.

Patient 2. A 30-year-old woman with a diagnosis of immune thrombocytopenic purpura had an incidental finding of fullness of the mediastinum on chest roentgenography. Subsequent computed tomography (CT) detected an isolated 5.8 × 6.6 × 8.0-cm soft-tissue mass adjacent to the trachea in the anterior mediastinum. The patient had no systemic or compressive symptoms. The remainder of her medical history was noncontributory.

Cervicomediastinal exploration under general anesthesia revealed 5.2 × 3.3 cm. No impingement of the esophagus or trachea was noted. Fine-needle aspiration cytology identified atypical mesenchymal-type cells in a background of lymphoid tissue, represented by a mixture of T and B cells, with the former predominating. Negative flow-cytometry results and the nonspecific nature of the cytologic findings did not permit a diagnosis of lymphoma.

The patient was taken to the operating room for excisional biopsy under general anesthesia. The subplatysmal mass was found to be adherent to the clavicle. Final pathology revealed the hyaline-vascular type of localized Castleman’s disease. The patient was referred for radiation therapy because of concerns about possible positive margins after excisional biopsy. At the 18-month follow-up, she had not experienced any complication or recurrence.

Patient 3. A 25-year-old woman presented to an outside clinic with a 6-week history of an enlarging left supraclavicular neck mass. The discovery of the mass had been preceded by numbness and tingling in her left arm and hand of 1 week’s duration. The patient had no complaints of airway compromise or dysphagia, and the remainder of her medical history was noncontributory. An open biopsy had resulted in a large amount of blood loss, and the patient required a transfusion. Pathology was consistent with Castleman’s disease, and the patient was referred to our institution for excision.

On physical examination, the mass was firm and located on the left side of the neck above the supraclavicular fossa. The mass deviated the trachea to the right. Contrast-enhanced CT of the neck and chest revealed that the 4 × 7-cm mass extended into the mediastinum (figure 1). The patient was scheduled for surgery under general anesthesia. Because she had lost so much blood during the earlier open biopsy, preoperative embolization was performed (figure 2). Intraoperatively, the mass was found to be lying directly on the left brachial plexus (figure 3, A), and it was removed without complication (figure 3, B). Histopathologic evaluation of the specimen confirmed that it was localized Castleman’s disease of the hyaline-vascular type (figure 4). At the 18-month follow-up, the patient remained disease-free with no symptoms of brachial plexus compression.

Discussion

Etiology. Numerous etiologies for Castleman’s disease have been proposed in the literature. Although its exact cause remains unknown, a mounting body of evidence indicates that a viral infection may make a significant contribution. Several studies have shown that there is an excessive amount of interleukin-6 (IL-6) production within Castleman’s disease lesions. The natural function of cytokine IL-6 is to increase the proliferation and survival of B cells. It is this lymphoproliferation of B cells that is the hallmark of Castleman’s disease.

Epidemiologic and polymerase chain reaction studies

### Table 1. Incidence of Castleman’s disease by location

<table>
<thead>
<tr>
<th>Location</th>
<th>Pct. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorax</td>
<td>60</td>
</tr>
<tr>
<td>Neck</td>
<td>14</td>
</tr>
<tr>
<td>Abdomen</td>
<td>11</td>
</tr>
<tr>
<td>Axilla</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
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</tbody>
</table>
have shown that Castleman’s disease is strongly associated with HHV8. The genome of this virus harbors an analog of the IL-6 gene. It has been proven that the introduction of HHV8 into mice via a retroviral vector causes polyclonal hypergammaglobulinemia with plasma-cell hyperplasia, and the resulting condition mimics multicentric Castleman’s disease. Furthermore, treatment of multicentric Castleman’s disease with monoclonal antibodies against IL-6 confers therapeutic benefits.

**Diagnosis.** At presentation, Castleman’s disease can pose several diagnostic dilemmas. Most often it manifests as an asymptomatic, unifocal, soft-tissue mass without any trademark signs or symptoms. Because of its nonspecific characteristics and the fact that it can mimic other neoplasms, it is often misdiagnosed.

Fine-needle aspiration cytology is typically nondiagnostic. In fact, the presence of lymphoid tissue in the aspirate may actually lead to a misdiagnosis of lymphoma. Keep in mind, however, that both the multicentric and unifocal forms have been associated with lymphoma.

With contrast, CT and MRI demonstrate a homogeneously enhancing mass. The enhancement is somewhat less pronounced in the plasma-cell type because it is less vascular. CT may exclude fatty or cystic masses, and the administration of contrast may prompt the surgeon to erroneously rule out the possibility of thymoma and lymphoma because these tumors generally do not enhance. Gallium scanning is of little help in diagnosing multicentric plasma-cell Castleman’s disease, although it is useful for detecting malignant lymphoma.

As a consequence of all these uncertainties, the differential diagnosis of Castleman’s disease is extensive (table 2). The most reliable way to establish a definitive diagnosis is by surgical resection and histopathologic confirmation. In the hyaline-vascular type of Castleman’s disease, the classic histopathologic findings are the presence of “burned-out” germinal centers and an “onion-skin” pattern of concentric expansion of the mantle zones. A single vessel is often...
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seen in the germinal center, and hyalinization (eosinophilic material) is often seen around the vessels. The plasma-cell type of Castleman’s disease is characterized by extensive proliferation of plasma cells around intact follicles. These unique histopathologic features of Castleman’s disease are easily recognized by pathologists who are familiar with this uncommon tumor.

Most patients experience a polyclonal lymphoproliferative process. When monoclonality develops, transformation to a malignant lymphoma must be suspected. Immunohistochemical and gene-rearrangement studies help identify those clonal cell populations.

Treatment. Careful staging following a histopathologic diagnosis is critical to proper treatment, and almost all cases will require therapy.

Most patients with unicentric Castleman’s disease can be treated with complete surgical ablation. Rare recurrences of localized cases have been associated with incomplete surgical removal. The masses in Castleman’s disease are quite vascular, so embolization before extirpation may reduce intraoperative bleeding and facilitate the excision. However, most cases are diagnosed only after surgical excision, so preoperative embolization is usually moot. For patients with localized disease that is not amenable to complete resection, radiation therapy may be successful.

Multicentric Castleman’s disease with systemic manifestations is more difficult to treat. A range of treatments is directed at palliation of symptoms. The results of radiotherapy have been inconsistent. Corticosteroids may be used in patients with disseminated disease. Combination chemotherapy is used in patients who do not respond to corticosteroids. Castleman’s disease is often treated with the same chemotherapeutic regimens that are used to treat lymphomas, but morbidity and mortality secondary to infections are high for patients who receive combined cyclophosphamide, vincristine, and prednisone; in such cases, referral to a medical oncologist is recommended. Erythropoietin can successfully treat associated severe anemia. Murine anti-IL-6 monoclonal antibody alleviates symptoms and dramatically improves abnormal laboratory values, although these abnormalities return upon cessation of therapy. The only complete remissions have been achieved with multiple-agent chemotherapy with or without steroids, with response rates as high as 93%. A trial of 60 to 100 mg of prednisone for weeks to months may also achieve a remission.

Biopsy may be required to assess whether multicentric Castleman’s disease is progressing despite treatment. Combined cyclophosphamide, vincristine, and prednisone or even a bone marrow transplant may be considered for patients with unresponsive, progressive disease. Follow-up is particularly important for patients with multicentric disease because of the potential for the development of malignancy or a fatal infection.

In conclusion, the astute clinician should be aware of Castleman’s disease and consider it in the differential diagnosis of any solid tumor that exhibits nonspecific presenting characteristics.

References

Table 2. Differential diagnosis of Castleman’s disease

<table>
<thead>
<tr>
<th>Mediastinum</th>
<th>Head and neck</th>
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<tbody>
<tr>
<td>Hypervascular metastasis</td>
<td>Carcinoma of the thyroid</td>
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<tr>
<td>Leiomyosarcoma</td>
<td>Cat scratch fever</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Epstein-Barr virus</td>
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<tr>
<td>Mediastinitis</td>
<td>Hodgkin’s disease</td>
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<td>Medullary carcinoma of the thyroid</td>
<td>Human immunodeficiency virus infection</td>
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<td>Lymphoma</td>
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<tr>
<td>Thymoma</td>
<td>Paraganglioma</td>
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<tr>
<td>Parathyroid adenoma</td>
<td>Schwannoma</td>
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</table>

Figure 4. Patient 3: Classic histopathology shows penetrating blood vessels and onion-skinning of the lymphocytes around an atrophic germinal center.

References