Absence of Gallium Uptake in Unicentric and Multicentric Castleman’s Disease

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Abstract

Castleman’s disease is a rare and poorly understood condition involving lymph nodes at various sites, predominantly in the mediastinum. Individuals with this disease often present with lymphadenopathy and general symptoms suggestive of lymphomatous disease, and they are at risk of developing malignant lymphoma. It is thus important to distinguish Castleman’s disease from other lymphoproliferative disorders. ⁶⁷Ga scintigraphy is a noninvasive and practical diagnostic tool for the investigation of patients with lymphoproliferative disorders. However, the value of this technique for the diagnosis of Castleman’s disease is not clear. Here, we describe five consecutive patients with various types of Castleman’s disease and show that none of these individuals exhibited ⁶⁷Ga uptake. Our results suggest the potential value of ⁶⁷Ga scintigraphy in both the diagnosis and management of Castleman’s disease.

Key words: Castleman’s disease, lymphoproliferative disorders, ⁶⁷Ga scintigraphy

Introduction

Castleman’s disease is a lymphoproliferative disorder that is uncommon, atypical, and of unknown etiology. It is characterized histologically by angiofollicular lymph node hyperplasia. Two clinical entities have been described: a unicentric presentation with disease confined to a single anatomic lymph node-bearing region and a multicentric presentation in which several sites are affected (1). Two basic histopathologic types of Castleman’s disease have also been distinguished, hyaline vascular and plasma cell, with the latter being less common. However, a clear separation of the two types is not always possible and a mixed type exists. Castleman’s disease of the hyaline vascular type is generally asymptomatic and is often discovered incidentally during routine physical examination, chest X-ray, or abdominal ultrasonography (2–4). Castleman’s disease of the plasma cell type is associated with systemic symptoms such as peripheral lymphadenopathy, asthenia, weight loss, fever, and anemia, most of which are a consequence of an increased production of interleukin-6 (IL-6) by the hyperplastic lymph nodes (2–7). Recently, Kaposi’s sarcoma-associated herpesvirus (also called human herpesvirus type 8, KSHV/HHV-8) was reported to be an etiologic agent of Castleman’s disease of the plasma cell type, especially in patients infected with human immunodeficiency virus (HIV) (8, 9).

⁶⁷Ga scintigraphy has proved effective for the early detection of lymphoproliferative disorders such as malignant lymphoma and has been proposed as a means of determining disease activity and prognosis (10). However, few data are available on ⁶⁷Ga uptake in individuals with Castleman’s disease. Here, we present ⁶⁷Ga scintigraphy findings for five pathologically proven cases of unicentric or multicentric Castleman’s disease.

Case Report

The clinical characteristics of the five individuals with Castleman’s disease are summarized in Tables 1 and 2. Two patients (cases 1 and 2) fulfilled the criteria for unicentric Castleman’s disease and underwent complete surgical resection of the mass (Table 1). Histological examination of the surgical specimens provided a diagnosis of hyaline vascular (Fig. 1C) and plasma cell types of the disease in cases 1 and 2, respectively. Case 1 (hyaline vascular type) was asymptomatic at presentation and her routine laboratory data were...
Figure 1. Unicentric Castleman’s disease of the hyaline vascular type in a 64-year-old asymptomatic woman. A, Contrast-enhanced chest CT image (mediastinal window), showing a well-defined mass with central calcifications in the middle mediastinum. B, Coronal T1-weighted MR image reveals a homogeneous mass in the middle mediastinum. C, Hematoxylin-eosin staining of a specimen of the resected mass, revealing that the mass was composed of lymphoid follicles containing deposits of hyaline and was transfixed by penetrating capillaries (original ×100). D, 67Ga scintigraphy was performed with a dual-head large rectangular field-of-view gamma camera (GCA 7200A-DI, GCA 90B, Toshiba). Whole body images were obtained 72 hours after injection of 111MBq of 67Ga citrate. Planar imaging on day 3 after 67Ga injection showing absence of abnormal 67Ga uptake.
Table 1. Characteristics of Patients with Unicentric Castleman’s Disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Disease site</th>
<th>Diagnostic procedure</th>
<th>Histopathology</th>
<th>Primary treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>F</td>
<td>None</td>
<td>Mediastinum</td>
<td>Surgical excision</td>
<td>HV</td>
<td>Resection</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>Anemia, fever</td>
<td>Mesenterium</td>
<td>Surgical excision</td>
<td>PC</td>
<td>Resection</td>
</tr>
</tbody>
</table>

HV: hyaline vascular, PC: plasma cell.

Table 2. Characteristics of Patients with Multicentric Castleman’s Disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Disease site</th>
<th>Diagnostic procedure</th>
<th>Histopathology</th>
<th>Primary treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>25</td>
<td>F</td>
<td>None</td>
<td>Mediastinum</td>
<td>VATS incision biopsy</td>
<td>HV</td>
<td>Steroid</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>F</td>
<td>Cough, fever</td>
<td>Mediastinum, hilum</td>
<td>VATS incision biopsy</td>
<td>PC</td>
<td>Steroid</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>M</td>
<td>Anemia</td>
<td>Mediastinum, hilum</td>
<td>VATS incision biopsy</td>
<td>PC</td>
<td>Anti-IL-6 therapy</td>
</tr>
</tbody>
</table>

Anti-IL-6: antibodies to IL-6.

normal. The lesion was discovered incidentally on chest radiographs. This patient remains symptom free after complete resection of the lesion (Fig. 1A and B). Case 2 (plasma cell type) was diagnosed with secondary amyloidosis by positive staining of the gastric mucosa with antibodies to serum amyloid protein A. The laboratory findings revealed severe anemia, an increased serum concentration of C-reactive protein, hypoalbuminemia, polyclonal hypergammaglobulinemia, and renal insufficiency. Computed tomography (CT) of the abdomen revealed a clearly bordered mass (5 by 4 cm) with small calcifications in the mesentery. With the exception of renal insufficiency, the laboratory data of the patient had improved by 4 months after surgical resection of the mass. In both patients with unicentric Castleman’s disease, $^{67}$Ga scintigraphy was performed before surgery but did not reveal abnormal uptake in either case (Fig. 1D).

Three patients (cases 3 to 5) met the criteria for multicentric Castleman’s disease (Table 2). Computed tomography of the chest revealed multiple enlarged mediastinal lymph nodes in case 3. Video-assisted thoracoscopic (VATS) biopsy of the mediastinal lymph nodes and histological analysis of the specimens provided a diagnosis of the hyaline vascular type of Castleman’s disease. In addition to multiple mediastinal and hilar lymphadenopathy, cases 4 and 5 were found by high-resolution CT to exhibit thickening of the peribronchovascular interstitium and interlobular septa as well as poorly defined glass-like opacities present in the centrilobular gland in a perilymphatic distribution (Fig. 2A and B). These two patients also had an increased serum concentration of IL-6 and hypergammaglobulinemia. Microscopic examination of mediastinal lymph node biopsy specimens obtained by VATS revealed typical features of the plasma cell type of Castleman’s disease (Fig. 2C). Plasma cell infiltrates showed polyclonal expression of light chains with no monoclonal component by immunohistochemical staining. Furthermore, histological examination of lung biopsy specimens revealed marked infiltration of B lymphocytes and plasma cells associated with the peribronchovascular and interlobular interstitia, whereas the alveolar septa appeared less involved, suggestive of a pulmonary manifestation of Castleman’s disease. We thus diagnosed both of these patients (cases 4 and 5) with Castleman’s disease of the plasma cell type with lymphocytic interstitial pneumonia of the lung. $^{67}$Ga scintigraphy was performed in all three patients with multicentric Castleman’s disease before surgical biopsy. The images showed no radionuclide accumulation in any region including the affected lymph nodes and lungs (Fig. 2D).

Discussion

Castleman’s disease was first described as a pathological entity in 1954 and was later defined by Castleman et al in 1956 (11). Diagnosis of Castleman’s disease is problematic given that histological analysis is usually required. Clinically, Castleman’s disease must be distinguished from reactive lymph node hyperplasia and malignant lymph node hyperplasia, and especially from malignant lymphoma, which is sometimes associated with this disease (12). Although $^{67}$Ga scintigraphy is often used to evaluate patients with lymphoproliferative disorders (10), few studies have described the application of this technique in individuals with Castleman’s disease.

We have now shown that two patients (cases 4 and 5) diagnosed with multicentric Castleman’s disease of the plasma cell type, a clinical entity with potential for malignant transformation, did not exhibit $^{67}$Ga uptake. These results are consistent with those of a recent study demonstrating the absence of $^{67}$Ga uptake in three cases of this type of Castleman’s disease (13). We also failed to detect $^{67}$Ga uptake in a rare case (case 2) of unicentric Castleman’s disease of the plasma cell type. Together, these observations suggest that the plasma cell type of Castleman’s disease is not detectable by $^{67}$Ga scintigraphy.
Figure 2. Multicentric Castleman's disease of the plasma cell type in a 53-year-old woman. A, Contrast-enhanced chest CT image (mediastinal window), showing enlarged mediastinal and hilar lymph nodes. B, Chest high-resolution computed tomography (HRCT) reveals thickening of the peribronchovascular interstitium, interlobular septa, and poorly defined centrilobular ground glass opacities that were perilymphatic in distribution. C, Hematoxylin-eosin staining of a specimen of the resected mass, revealing marked interfollicular infiltration by plasma cells (original ×400). D, $^{67}$Ga scintigraphy was performed as described in Fig. 1. Planar images on day 3 after $^{67}$Ga injection demonstrate no $^{67}$Ga uptake.
The hyaline vascular type of Castleman’s disease, the more common of the two histopathologic types, is usually apparent in the thorax, although it can manifest at any site where lymph nodes are normally present (1–3). In the present study, 67Ga scintigraphy yielded negative results for the two patients (cases 1 and 3) with the hyaline vascular type of Castleman’s disease in the mediastinum. A review of studies published in English from 1966 onward revealed one report that failed to detect 67Ga uptake in a patient with the hyaline vascular type of Castleman’s disease and two reports each detecting 67Ga uptake in one such patient (14–16). One of the two previous 67Ga uptake-positive patients showed unusual histological features with a predominance of the hyaline vascular type of disease (16). Given the small sample size, it is not possible to explain the variance in 67Ga uptake in these patients. The positive 67Ga uptake previously observed in such patients may have resulted from chronic infection including mycobacteriosis. Further studies with larger numbers of patients are required to resolve this issue.

In the present study, none of the five cases of Castleman’s disease manifested 67Ga uptake. Our results suggest that 67Ga uptake does not occur in either type of this disease. The mechanisms regulating 67Ga uptake by tumor cells have been found to be partially dependent on the expression of the transferrin receptor (CD71) in these cells (10, 17). Transferrin receptor is also expressed in activated or proliferating lymphocytes and thus is more frequently expressed in high grade than in low grade lymphomas. A low density of activated lymphocytes at the involved sites may result in the absence of 67Ga uptake in the patients with Castleman’s disease. Although Castleman’s disease remains a diagnostic challenge in the absence of histological evaluation, 67Ga scintigraphy may help to narrow the diagnostic possibilities. With regard to the association between malignant lymphoma and Castleman’s disease, non-Hodgkin’s lymphoma is the most often associated with the multicentric presentation and Hodgkin’s disease with the unicentric presentation (12). In a previous study of human immunodeficiency virus-positive patients with lymphadenopathy, those individuals that manifested 67Ga uptake in lymph nodes were found to have tuberculosis or lymphoma, whereas those who did not exhibit 67Ga uptake had reactive follicular hyperplasia, suggesting a specificity of 67Ga uptake for lymphoma (18). Together, these observations suggest that 67Ga scintigraphy, as a noninvasive tool, might be of value in the early detection of malignant lymphomas that develop during the course of Castleman’s disease.

References