Extranodal Castleman Disease of the Extremities: A Case Report and Review of the Literature

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CASE REPORT

INTRODUCTION

Between 1954 and 1956, Benjamin Castleman1,2 reported a series of 13 unusual patients with enlarged mediastinal lymph nodes resembling and erroneously classified as thymoma. Castleman eloquently described the histological distinction of these tumors from other lymphoproliferative disorders2 and neoplasms. Since this original description, the lymphoproliferative disorder now known as Castleman disease (CD) has been called follicular lymphoreticuloma, giant lymph node hyperplasia, angiomatous lymphoid hamartoma and angiofollicular lymph node hyperplasia.3 The patients in Castleman’s original series exhibited multiple mediastinal masses with two consistent, prominent features: Hyperplasia of lymphoid follicles and marked capillary proliferation with endothelial hyperplasia.2 The latter feature likely accounted for the “excessive bleeding” encountered by the surgical team. Each of the original 13 patients had localized disease or unicentric Castleman disease (UCD). In 1978, Gaba4 et al reported a patient with multiple retroperitoneal and axillary lesions histologically similar to Castleman’s series, thus providing the first example of multicentric Castleman disease (MCD).

In recent years, there has been an expanded interest in Castleman disease as it has been associated with a variety of malignancies, including follicular dendritic cell sarcoma, Kaposi’s sarcoma (KS), non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, and POEMS syndrome as well as with the human immunodeficiency virus (HIV) and human herpesvirus 8 (HHV-8).5-9 The modern conspectus regards Castleman disease as a lymphoproliferative lesion of unknown etiology whose unicentric and multicentric forms have two histopathologic variants: hyaline vascular Castleman disease (HVCD) and plasma cell Castleman disease (PCCD). Of the two histological variants, HVCD accounts for 90% of cases and most commonly presents as a mediastinal nodal mass.2,10-12 Extranodal Castleman disease occurs with the majority of masses located in the mediastinum or retroperitoneum.13-16 Very few cases of Castleman disease in the extremities have been reported in the English literature.10-12,17-19

We report a case of HVCD presenting as a muscular forearm mass. The correct diagnosis was not obtained until 7 months after initial presentation. HVCD was not included in the original radiological differential diagnosis. We will discuss the pathological and radiological features that allow for the recognition of Castleman disease and its distinction from other tumors and lymphoproliferative disorders. Importantly, we aim to raise awareness of this condition in regard to the radiological and clinicopathological differential diagnosis of muscular masses.

CASE REPORT

A 76-year-old woman was referred to the Duke University Medical Center Orthopaedic Oncology Service with a left forearm mass noticed several months prior. The mass was painful when first noticed but the pain did not persist. No inciting events were associated with the appearance of the mass. An incisional biopsy performed by the referring physician suggesting an atypical lymphoid neoplasm prompted her referral. The patient had a history of left carpal tunnel syndrome and had undergone a left carpal tunnel release several years prior; she was without symptoms related to this. The family history did not suggest the presence of any familial disease.

Upon examination, a mass was readily palpable on the mid-volar aspect of her left forearm. It was solitary, firm, mobile, nontender and without associated lymphadenopathy. There were no abnormal findings upon neurovascular examination, and the patient demonstrated full strength and nontender range of motion from the shoulder to the fingers. Laboratory studies revealed no abnormal findings.

Conventional radiographs revealed a soft tissue mass in the volar compartment of the right forearm with annular and reticular mineralizations scattered about its center (Figs 1A and B). CT scan further characterized these mineralizations as coarse punctate to radial densities seen exclusively in the central...
portion of the mass (Figs 2A and B). MRI of the left forearm (Figs 3A to D) demonstrated the mass to have the following features: 6.3 × 2.7 × 4.3 cm in measurement, heterogeneous high signal intensity on T1-weighted images and hypointense to surrounding muscle on T2-weighted images. Following administration of gadolinium, there was diffuse signal enhancement throughout the mass, but less intense centrally, giving the appearance of a ‘target’. Other distinct features of the mass seen on MR imaging included peritumoral fat, tortuous tubular structures consistent with prominent vessels coursing through the fat and central fibrosis (Figs 3A to D). Void flows were visible within the fatty tissue at both longitudinal poles of the mass. 18F-FDG PET/CT (Figs 4A and B) demonstrated a hypermetabolic forearm mass without other abnormalities. Chest radiographs demonstrated no mediastinal or hilar enlargement.

Incisional biopsies had been performed on two occasions by referring physicians. Specimens had been sent to multiple pathologists with no diagnostic consensus reached. These were reviewed by our pathology staff. Prior histopathologic assessments had ranged from “atypical lymphoid neoplasm” to “soft tissue with nonspecific changes insufficient for diagnosis of lymphoproliferative disorder.” Descriptively, lymphoid follicles were identified within the specimens, consisting of atypical lymphocytes with scattered cells staining for CD3, CD5, CD20, and CD43 without morphologic evidence of lymphoma. CD10 and CD23-staining cells highlighted small germinal centers. BCL-2 was negative in the germinal centers. Upon T-cell gamma chain PCR analysis, no clonal T-cell population was identified. B-cell PCR analysis was likewise negative.

In light of the nondiagnostic nature of the prior evaluations, marginal excisional biopsy was performed, revealing a well-circumscribed, tan, firm, intramuscular mass within the volar flexor compartment. Microscopic examination of permanent sections showed a capsulated mass separated from the surrounding skeletal muscle by a vascularized stroma (Fig. 5A). There were moderate size vessels in the connective tissue surrounding the mass (Fig. 5A) and at the periphery of the mass, which penetrated the deeper portions of the mass along fibrous septa (Fig. 5B). The mass was composed of lymphoid follicles of variable size and shape with intervening diffuse collections of mononuclear cells (Figs 5C and D). Medium size vessels and a plethora of capillaries were present in the diffuse interfollicular areas (Figs 5E and F) along with many polyclonal plasma cells (Figs G and H). Flow cytometric examination did not show monoclonal B-cells or phenotypically abnormal T-cells, although a very high CD4:CD8 ratio prompted a T-cell gene rearrangement study which was negative. Based on these features, a diagnosis of hyaline vascular type of Castleman disease was rendered and a definitive resection of the remaining mass and tumor bed was performed. Microscopic examination again showed HVCD without involvement of the resection margins. In 30 months of follow-up, the patient has been without recurrent symptoms or masses.

**DISCUSSION**

Castleman disease is a well-recognized entity, uncommonly seen in the extremities, with characteristic radiological features. This patient presented with a soft tissue mass which displayed the radiological, gross and histopathological features typical of
hyaline vascular Castleman disease (HVCD). However, it was not considered in the original radiological differential diagnosis. When extranodal Castleman disease occurs, it is almost always in the mediastinum or retroperitoneum.\textsuperscript{14,15} Other locations of extranodal Castleman disease reported in the literature include the vulva, nasopharynx, larynx and pancreas.\textsuperscript{23-26} Castleman disease presenting as an isolated soft tissue mass in the extremities is exceptionally uncommon.\textsuperscript{10-12,17-19} There have been only seven other cases reported in the literature, the salient features of which are presented in Table 1.

Castleman disease of the extremities is exclusively represented by the hyaline vascular type. Our patient is unusual because of her advanced age. The mean age of the seven previously reported cases is 18 (range: 15 months to 29 years).

Figs 3A to D: Multiple magnetic resonance images of the left forearm heterogeneous high signal intensity on T1-weighted images (B and C), and hypointensity relative to surrounding muscle on T2-weighted images (A and D). Following administration of gadolinium, there was diffuse signal enhancement throughout the mass, but less intense centrally, giving the appearance of a ‘target’ (B). Also visible are the hallmark findings of perilumoral fat, prominent vessels and central fibrosis.

Figs 4A and B: Coronal (A) and axial (B) fused PET images demonstrating a hypermetabolic forearm mass.
Figs 5A to H: Histopathology of forearm mass after definitive wide resection. (A) A capsule (arrowheads), vascular connective tissue and fat (short arrows) separate the mass from surrounding skeletal muscle (long arrows) (H&E, 40x), (B) moderate size vessels are present at the periphery of the mass (arrowhead) and penetrate the deeper portions of the mass along fibrous septa (arrows). (H&E, 40x), (C and D) lymphoid follicles of variable size and shape (arrowheads) and diffuse interfollicular areas are present. Follicular dendritic cells stain with CD21 antibody in D (H&E, 40x and CD21, 40x), (E and F) medium size vessels and capillaries in the diffuse interfollicular areas are accentuated by staining of endothelial cells (CD31, 40x and 200x), (G and H) polyclonal plasma cells in the diffuse interfollicular areas are accentuated by staining for immunoglobulin light chains (Kappa and Lambda, 200x).
Six out of the seven patients were female. Four masses were located in the lower extremity, and three were located in the upper extremity. There appears to be a predilection for the proximal portion of the extremity. With the exception of our mass being located in the forearm, the other seven masses were either in the thigh or the arm. All masses were excised. Follow-up data was not available for three patients. The other seven patients remained disease-free for the duration of follow-up (up to 13 years). Description of radiological findings is sparse. Plain radiographic and CT imaging were not previously described (Table 1).

With regard to the radiological features of CD in general, the early literature defined the radiographic and angiographic,\textsuperscript{27} computed tomography,\textsuperscript{28,29} and ultrasound features,\textsuperscript{30} primarily of the nodal and localized CD. More recently, MRI\textsuperscript{31-33} and PET\textsuperscript{34,35} have further characterized the nodal, localized, diffuse, and extranodal forms of CD. PET/CT, in particular, as a whole-body, molecular-morphologic imaging modality, plays a significant role in diagnosing MCD and assessing bone marrow involvement. Staging, re-staging, and evaluation of treatment response of patients with MCD have been reported.\textsuperscript{36,37} In the following paragraphs, we review the literature with regard to specific radiographic findings in CD.

### Shape, Size and Enhancement

Nodal UCD in the neck, thorax and abdomen typically presents with an ovoid or circular single mass and occasionally as a dominant mass with several enlarged regional lymph nodes.\textsuperscript{24,30} The maximum reported diameter of a CD mass varies with the largest being 25 cm in the thorax\textsuperscript{32} and 18 cm in the abdomen.\textsuperscript{29} The median size in the largest series was 6.8 cm in the thorax\textsuperscript{32} and 5.6 cm in the abdomen.\textsuperscript{29} The size of extranodal muscular UCD is considerably smaller—reported from 2 to 5 cm. Our patient’s intermuscular forearm mass, measuring $6.3 \times 4.3$ cm, is the largest extranodal muscular mass reported.

In the neck, thorax, abdomen and pelvis, the CT, MRI and ultrasound (US) characteristics of nodal UCD are closely related to the size as well as the histopathology of the mass.\textsuperscript{29,38} Lesions smaller than 5 cm in diameter are typically more homogeneous on US, CT, and MRI when compared to masses greater than 5 cm in diameter. Smaller masses are homogeneously isodense on unenhanced CT and vary from moderate to high enhancement after contrast administration. On MRI, smaller masses tend to be isointense or hypointense to muscle on T1-weighted images and hyperintense to muscle on T2-weighted images.\textsuperscript{38} Conversely, nodal UCD masses above 5 cm, regardless of the anatomic location frequently have intraläsional calcification, fibrosis, cystic degeneration or necrosis, imparting a more heterogeneous architecture to the imaging of the mass, regardless of the imaging modality.\textsuperscript{29,32,34} The rich, diffuse vascular network—a distinctive histologic feature of CD, particularly the hyaline vascular (HVCD) type—is the main reason for enhancement. Approximately 90% of all nodal CD are HVCD variant.

Less commonly, patterns of contrast enhancement are related to cystic necrotic degeneration. Zhou reported necrosis in 22% of nine abdominal UCD cases.\textsuperscript{38} This particular investigator suggests the low incidence of necrosis in the face of typically rapid tumor growth is related to the hypervascularity, good collateral circulation and low susceptibility of lymphoid

<table>
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<tr>
<th>Author(s)</th>
<th>Age/sex</th>
<th>Symptom</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Plain</th>
<th>MRI</th>
<th>Subtype</th>
<th>Therapy</th>
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<td>Rooney et al\textsuperscript{12}</td>
<td>15 months/ female</td>
<td>Painless mass</td>
<td>Thigh (biceps femoris)</td>
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<td>HV</td>
<td>Excision</td>
<td>DF, 1 year</td>
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<td>Fiel-Gan et al\textsuperscript{11}</td>
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<td>Arm (triceps)</td>
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<td>Hyperintense to muscle</td>
<td>HV</td>
<td>Wide resection</td>
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<td>18 years/ female</td>
<td>NA</td>
<td>Proximal thigh</td>
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<td>NA</td>
<td>NA</td>
<td>HV</td>
<td>Excision</td>
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<td>NA</td>
<td>Thigh</td>
<td>$5.5 \times 3.0 \times 2.0$</td>
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<td>Hyperintense to muscle; hypervascular</td>
<td>HV</td>
<td>Excision</td>
<td>DF 3 years</td>
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<tr>
<td>Edward et al (present case)</td>
<td>76 years/ female</td>
<td>Painful mass</td>
<td>Left volar forearm</td>
<td>$6.3 \times 2.7 \times 4.3$</td>
<td>Reticular mineralizations</td>
<td>Hypervascular</td>
<td>Marginal excision</td>
<td>DF 3 years</td>
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NA – Not available or not specified; DF – Disease free
follicles to necrosis. Multiple authors have reported peripheral or rim-like enhancement on CT and MRI, explained by the histological abundance of small vessels in the periphery of the mass immediately deep to the capsule.

**Calcification**

Characteristic intrallesional calcifications of nodal and extranodal UCD have been documented by conventional radiography, US, CT and MRI in the thorax and abdomen. Yamasita, in a review of the early radiologic literature on CD (23 patients), found an incidence of calcification of 25% for both forms of CD. McAdams reported an incidence of 20% for calcification in thoracic lesions. In the abdomen and pelvis, calcification is more prevalent, reported at rates between 31 and 50%. To our knowledge, there are no reports in the literature of CD calcifications in the neck, axilla or somatic soft tissues. Calcifications typically involve the center and less often the periphery of the mass and are usually small. The largest calcification reported, measuring 3.2 cm, was centrally located in a large lesion in the tail of the pancreas. These calcifications, histologically are found most often in the larger UCD masses at the interfolllicular apices, within large fibrotic areas around the prominent capillaries and hyalinization typical of HVCD. These microscopic perivascular findings are reflected in the distinctive punctate and arborizing calcification patterns of CD seen on imaging. In our patient, these features were present on all images but best appreciated on conventional radiographs and CT (Figs 1 and 2). On MR imaging, discrete, round, voided-signal foci isointense to cortical bone correlated well with the intrallesional CT calcifications.

**Fibrosis**

The uncalcified stromal collagen bundles seen on histopathology correlated with central radial or stellate low densities on CT and intermediate signal intensities on MRI. These histopathological features are typical of UCD, and the correlative imaging findings have been described as characteristic of UCD masses encountered in the abdomen and pelvis.

**Feeding Vessels**

Internal capillary hyperplasia, a rich subcapsular vascular network and the presence of large vessels at the periphery are characteristic histopathological features of UCD masses. Therefore, it is not surprising that the presence of large feeding vessels surrounding these masses has been well-described in the radiological literature in extramucosal UCD on MRI, CT, ultrasound and angiography. The patient presented in this paper displayed all of the imaging features characteristic of CD, yet because of the unusual location, CD was not included on the original radiological differential diagnosis. The patient underwent two incisional biopsies with a resultant panoply of tissue diagnoses, including lipoma, lymphoma, atypical lymphoid hyperplasia, normal soft tissue and ectopic lymphoid infiltrate of skeletal muscle, before the correct diagnosis was obtained by means of excisional biopsy. As localized Castleman disease is treated with surgical resection, which is usually curative, the patient’s 7-month course from presentation to definitive resection would have been altered considerably given a correct diagnosis earlier in the course of clinical evaluation.

Additionally, it is important to recognize and diagnose Castleman disease because of its potential for transformation into follicular dendritic cell sarcoma, an intermediate grade malignancy. The presence of dysplastic follicular dendritic cells within the follicles of HVCD masses was first described in 1991. Chan and others have subsequently described the transformation of follicular cells in Castleman disease into follicular dendritic cell sarcoma, including the report of a patient whose malignant transformation was traced by sequential biopsies. While other types of extranodal Castleman disease have generally not recurred after surgical excision, there is one report of a patient with a nasopharyngeal HVCD mass which recurred 8 years after excision. This same patient developed a follicular dendritic cell sarcoma 11 years after excision of the primary.

In summary, extranodal Castleman disease can be a challenging diagnosis to make, especially when it presents in an unusual location. We have described the radiographic findings which should prompt inclusion of Castleman disease in the differential diagnosis of soft tissue masses. It is hoped that this report will stimulate the consideration of Castleman disease when atypical soft tissue masses of the extremities are encountered.

**REFERENCES**

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