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FULL PAPER

Multimodality imaging and clinical features in Castleman disease: single institute experience in 30 patients

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Objective: To analyse imaging features of subtypes of Castleman disease (CD), emphasizing differentiating features from lymphoma.

Methods: Institutional review board-approved, Health Insurance Portability and Accountability Act compliant, retrospective study examined 30 patients with CD. 30 patients (females, 20; mean age, 46 years; range, 22–87 years) with histopathologically confirmed CD and pre-treatment imaging formed the analytic cohort. Imaging at presentation in all patients [CT, 30; positron emission tomography (PET)/CT, 5; MR, 4; ultrasound, 3] and subsequent imaging in three cases that developed lymphoma was reviewed by two radiologists in consensus.

Results: Subtypes: hyaline-vascular ($n=18$); multicentric not otherwise specified (NOS) ($n=6$); human herpesvirus 8 associated ($n=2$); mixed unicentric ($n=2$); pure plasma-cell variant ($n=1$); and unicentric NOS ($n=1$). Distribution: unicentric ($n=17$); and multicentric ($n=13$). Nodal sites—unicentric: 13 thoracic, 3 abdominal and 1 cervical; multicentric: 9 abdominal, 8 thoracic, 6 cervical, 5 inguinal, 4 axillary and 4 supraclavicular. On CT,

differentiating features from lymphoma were calcification ($n=8$; 26.7%) and heterogeneous enhancement ($n=5$; 19.2%). No association between CD subtype, degree or enhancement pattern, or calcification was noted. On PET/CT ($n=5$), nodes were typically fluorine-18 fludeoxyglucose avid ($n=4$). On ultrasound ($n=3$), nodes were hypoechoic, homogeneous with posterior acoustic enhancement. On MR ($n=4$), nodes were hypointense ($n=2$) to isointense ($n=2$) on T_1 weighted images and isointense ($n=1$) to hyperintense ($n=3$) on T_2 weighted images. All ($n=4$) demonstrated homogeneous enhancement. Three cases developed non-Hodgkin's lymphoma, two of the three had larger spleens, and these cases had effusions/ascites.

Conclusion: CD can be unicentric or multicentric and involve nodes above and below the diaphragm. Patients with CD can develop lymphoma.

Advances in knowledge: Assessing individual risk of developing lymphoma in patients with CD is difficult, although the findings of splenomegaly, pleural effusion and ascites may be suggestive.

Castleman disease (CD) is a rare cause of lymphadenopathy that was first described in 1954 by Benjamin Castleman, as hyperplasia of mediastinal lymph nodes, with “many germinal centres containing hyalinized foci and surrounded by mature lymphocytes”.¹ This classic description became known as the “hyaline-vascular type” of CD. Keller et al² subsequently described the “plasma cell type” in 1972 based on the discovery of a plasma cell rich variant by Flendrig and Schillings.³ Later studies showed that CD occurs not only as a localized process (unicentric) but also in a multicentric (more than one site) distribution. A variant of the multicentric form was later found to be associated with human herpesvirus 8 (HHV-8), the same virus found in Kaposi's sarcoma. Similar to Kaposi's

sarcoma, it is often identified in patients with the human immunodeficiency virus (HIV).⁴ The classification of CD has been restructured in pathology literature, as reviewed by Cronin and Warnke⁴ in 2009, integrating a histopathogenic approach with the established distributive model (unicentric vs multicentric).

The four subtypes of CD as reviewed by Cronin and Warnke⁴ include: (1) hyaline-vascular CD, (2) plasma cell CD, (3) HHV-8-associated (plasmablastic) multicentric CD (MCD) and (4) MCD, not otherwise specified (NOS). The hyaline-vascular subtype typically occurs as a unicentric process, involving a single node or local group of nodes. The plasma-cell variety, characterized by sheets of mature plasma

cells in the interfollicular tissue, occurs more often as a multicentric process.² Patients with HHV-8-associated (plasmablastic) MCD incur a unique risk of developing HHV-8-positive plasmablastic lymphoma.⁵ The multicentric-NOS variant is a waste-basket term used to classify multicentric cases that are HHV-8 negative and/or those that show intermediate histopathology (such as mixed features of both plasma-cell and hyaline-vascular). The pathogenesis of CD remains unclear, although important associations have been discovered, such increased serum levels of interleukin (IL)-6, which is believed to mediate the mechanism of lymphoproliferation in CD.⁶ The expression of a viral analogue of IL-6 (vIL-6) by HHV-8 may play a role in the downstream mediation of plasmacytosis in the setting of HHV-8 infection, with approximately 50% similarity to the human IL-6 gene on an amino acid level.⁷

The radiological appearance of CD in various parts of the body has been described in the literature.^{8–11} CD occurs, with overlap, throughout the body, most commonly in the chest (70%), neck (40%), abdomen and pelvis (12%) and axilla (4%).¹² The median age of diagnosis is in the fourth decade, occurring equally among males and females.⁴ The presentation of the disease is variable, and depending on the subtype, CD can present along the spectrum of an asymptomatic, localized nodal mass, often discovered incidentally, to multifocal adenopathy with B-symptoms and haematological derangements that clinically mimic lymphoma. The purpose of this study was to characterize the multimodality imaging features of CD, with emphasis on the appearance of defined subtypes, and to identify imaging features that may be helpful in distinguishing CD from lymphoma. Furthermore, in the rare cases of CD that developed lymphoma, we attempted to identify findings at imaging that distinguished these cases.

METHODS AND MATERIALS

Subjects

This was a Health Insurance Portability and Accountability Act-compliant, institutional review board-approved, retrospective study. We identified 53 consecutive patients with a diagnosis of CD seen at Dana-Farber Cancer institute between 1997 and 2012. 30 of the 53 patients had available pre-treatment imaging. In all cases, the histopathology of these patients had been confirmed by review of pathology reports to verify the diagnosis of CD.

Imaging

Pre-treatment imaging included CT examinations in 30 patients, positron emission tomography (PET)/CT in 5 patients, MR in 4 patients and ultrasound in 3 patients. 12/30 patients had non-contrast- and contrast-enhanced CT scans. 14/30 patients had contrast-enhanced CT scans only. 4/30 patients had only non-contrast CT scans. Two of the non-contrast studies were obtained as part of PET/CT studies: one was performed at an outside institution and one was performed in 2003, at which time departmental standard protocol was a non-contrast chest CT if there was no known cancer diagnosis in the patient. 35/42 CT scans were performed at our institution. Outside studies were uploaded into picture archiving and communication system (PACS) and reviewed on Centricity PACS RA1000 (GE Healthcare, Barrington, IL)

workstation. CT scans at our institution were performed on multidetector scanners [4-slice (GE Healthcare), 16-row (Siemens Medical Solutions, Forchheim, Germany) and 64-row (Toshiba America Medical Systems, Tustin, CA) multidetector CT systems with 0.5-mm collimation, 120 kVp, 500 mA (maximum), gantry rotation time of 0.5 s, and table speed of 26.5 mm per rotation] using standard algorithms with 5-mm axial and 4-mm coronal reconstructions. In patients who received intravenous contrast, 75–100 ml of iopromide [300 mg I ml⁻¹; Ultravist® 300 (Bayer HealthCare Pharmaceuticals, San Francisco, CA)] was administered with an automated injector (Stellant®; Medrad Inc., Warrendale, PA) at a rate of 2–3 ml s⁻¹, with a scan delay of 40–60 s. All CT images were reviewed on a Centricity PACS RA1000 workstation.

The MR images were acquired as per the following protocols: head/neck—axial/coronal T_1 spin echo [repetition time (TR)/echo time (TE), 800/13 ms], axial fluid-attenuated inversion recovery (FLAIR) T_1 (TR/TE, 2800/9.2 ms), axial/coronal FLAIR T_2 (TR/TE, 9000/129 ms), axial T_2 fast spin echo (TR/TE, 4150/76.6 ms), axial/sagittal post-gadolinium T_1 ; abdomen—axial T_2 (TR/TE, 1866/81 ms), T_2 FSE (TR/TE, 2000/98 ms), in- and out-of-phase T_1 , pre- and post-gadolinium fat suppressed T_1 weighted (TR/TE, 5.1/2.1 ms) dynamic three-dimensional gradient recalled echo images; pelvis—axial T_2 (TR/TE, 1956/86 ms), axial and coronal short tau inversion recovery, in- and out-of-phase T_1 , pre- and post-gadolinium fat suppressed T_1 weighted (TR/TE, 5.8/2.5 ms) images. All four MR examinations were performed with gadolinium administration. In patients receiving contrast, gadolinium was administered at doses of 0.1 mmol kg⁻¹ body weight up to a maximum dose of 20 ml.

5/5 PET/CT scans were performed at our institution at the time of CD diagnosis. PET/CT scans at our institution were performed after at least 4 h of fasting and after ensuring normal blood glucose on the day of the examination. Approximately, 60 min following intravenous tracer administration (10–14 mCi) via a peripheral vein, PET imaging was performed from the base of the skull through the thighs (Discovery LS; GE Healthcare, Waukesha, WI; or Biograph® 16-HiRes; Siemens Healthcare, Erlangen, Germany). Non-contrast helical CT imaging (5-mm thickness axial images) was performed over the same range without breath-hold for attenuation correction of PET images and anatomic correlation. All PET/CT images were reviewed on HERMES GOLD™ (Hermes Medical Solutions Inc., Greenville, NC) workstation.

The ultrasound examinations in all three patients were performed at outside institutions, and the images were uploaded into PACS and reviewed on Centricity PACS RA1000 workstation.

Image analysis

Two radiologists, with 2 and 10 years' experience, respectively, reviewed available imaging in consensus. The following pre-treatment imaging features were recorded as found on CT: location/nodal station, distribution of nodes (unicentric vs multicentric), largest dimension of nodes (measured as longest axis in a transverse or craniocaudal dimension from axial or

coronal images), homogeneous or heterogeneous appearance of the nodes, attenuation on CT for pre- and post-contrast images (when available), node-to-muscle attenuation ratio (ratio of attenuation of nodal involvement compared with skeletal muscle), the presence or absence of nodal enhancement (defined as node-to-muscle enhancement ratio >1), nodal enhancement pattern (homogeneous *vs* heterogeneous), the presence of nodal calcification, pattern of nodal calcification (punctate, coarse or arborizing), the presence of ascites, the presence of pleural effusion, liver size (maximum transverse or craniocaudal dimension) and spleen size (maximum transverse, anteroposterior or craniocaudal dimension).

Unicentric disease was defined as nodal enlargement confined to one anatomical nodal station or centred at one anatomical nodal station extending into an adjacent station (e.g. a middle mediastinum nodal mass extending into the anterior mediastinum and/or hilum). Multicentric disease was defined as nodal enlargement at more than one nodal station or multiple separate enlarged nodes at one nodal station (e.g. multiple enlarged mesenteric nodes).

The following pre-treatment imaging features were recorded on PET/CT: distribution of nodes, maximum standardized uptake value (SUV_{max}) of nodes and visceral involvement. The following pre-treatment imaging features were recorded on ultrasound: echogenicity compared with the surrounding soft tissue, the presence of internal septations, the presence of shadowing echogenic foci suggestive of calcification, posterior acoustic enhancement (enhanced through transmission) and the presence of internal flow with Doppler interrogation. The following pre-treatment imaging features were recorded on MR: signal intensity on T_1 and T_2 weighted sequences relative to muscle, the presence of enhancement and enhancement pattern (homogeneous *vs* heterogeneous).

In patients with pathologically confirmed CD that later developed lymphoma, CT imaging at the time of lymphoma diagnosis was evaluated for change in spleen size, the presence or absence of pleural effusion or ascites, maximum nodal size, nodal-to-muscle attenuation ratio of enlarged nodes and number of sites of lymphadenopathy, heterogeneity of enhancement and nodal stranding.

Clinical data

The following pre-treatment clinical and laboratory information, when available, was recorded from the electronic medical record: presenting symptom(s), haemoglobin, haematocrit, HIV status, erythrocyte sedimentation rate, C-reactive protein (CRP) and IL-6 level. When available, pleural or peritoneal fluid cytology and chemistries were analysed. In cases of those who developed lymphoma, new or worsening symptoms from the time of CD diagnosis were recorded.

Histopathology data

The individual subtypes were recorded from pathology reports in the electronic medical record. All pathology reports from each patient prior and subsequent to the diagnosis of CD were reviewed. The development of lymphoma, subtype of lymphoma and time to lymphoma diagnosis from diagnosis of CD were recorded.

RESULTS

The study population consisted of 20 females and 10 males with a mean age of 46 years (range, 22–87 years). The mean age of the females was 45 years. The mean age of the males was 49 years.

Subtypes of Castleman disease

Of the 30 patients, 18 (60%) patients had hyaline-vascular CD, 6 (20%) patients had multicentric NOS, 2 (6.7%) patients had HHV-8-associated disease and 1 (3.3%) patient had pure plasma-cell variant. In addition, three patients had histological and distributive features that, when combined, did not fit into the updated subtypes. Two patients had mixed histopathology (hyaline vascular and plasma cell) in a unicentric distribution—an apparent “mixed unicentric” picture, which falls outside of the updated subtypes. One patient had histopathology “within the spectrum of CD” with atypical features (see the Discussion section) in a unicentric distribution—an apparent “unicentric NOS” picture, which falls outside of the updated subtypes.

With respect to distribution, 17 (56.7%) patients had unicentric disease and 13 (43.3%) patients had multicentric disease. Of the 17 patients with unicentric disease, 14 (82.4%) were classified as pure hyaline-vascular variant and 3 fell outside the updated subtypes (as above). Of the 13 patients with multicentric disease, 6 (46.2%) were classified as multicentric NOS, 4 (30.8%) were classified as pure hyaline-vascular, 2 were HHV-8-associated and 1 was classified as pure plasma cell variant.

Anatomic distribution

Of the 17 patients with unicentric disease, the anatomic nodal distribution on imaging was as follows: 13 thoracic, 3 abdominal and 1 cervical. Unicentric thoracic nodal involvement ($n = 13$) was distributed, with compartmental overlap, as follows: five middle mediastinal, five hilar, four anterior mediastinal and one cardiophrenic angle involvement. Unicentric abdominal nodal involvement was distributed as follows: two retroperitoneal and one mesenteric. None of the patients had isolated inguinal, supraclavicular or axillary nodal CD.

Of the 13 patients with multicentric disease, the anatomic nodal distribution on imaging was as follows: 9 abdominal, 8 thoracic, 6 head and neck, 5 inguinal, 4 axillary and 4 supraclavicular. Breakdown of involved sites in thoracic disease ($n = 8$) was as follows: eight middle mediastinal, five hilar and two anterior mediastinal. Breakdown of involved sites in abdominal disease ($n = 9$) was as follows: seven retroperitoneal, five mesenteric, five iliac and two periportal.

There were no cases primarily involving the lung parenchyma or the chest wall. Three patients with thoracic disease had pleural effusions at presentation, all of which had multicentric disease. There was no abdominal organ involvement in any patient seen by imaging. One patient had ascites at presentation, occurring in the setting of multicentric disease.

Clinical features

The following presenting symptoms were found in the 30 patients: 11 with cough, 9 with pain, 8 with dyspnoea, 5 with haemoptysis, 5 with “B symptoms” (defined as fever, chills and/or night sweats),

Table 1. Laboratory values at time of Castleman disease (CD) diagnosis

Laboratory test	Mean	Median	Range	Reference
Haemoglobin, g dl ⁻¹ (<i>n</i> = 28)	12.6	12.7	9.9–15.7	11.9–15.0
UCD (<i>n</i> = 16)	13.1	13.3		
MCD (<i>n</i> = 12)	12.0	11.8		
Haematocrit, % (<i>n</i> = 28)	37.2	37.6	25.8–44.0	34.8–43.6
UCD (<i>n</i> = 16)	38.6	39.0		
MCD (<i>n</i> = 12)	35.4	33.1		
C-reactive protein, mg l ⁻¹ (<i>n</i> = 16)	22.0	8.0	0–108.9	0–7.9
UCD (<i>n</i> = 9)	4.6	1.5		
MCD (<i>n</i> = 7)	44.3	47.2		
Interleukin-6, pg ml ⁻¹ (<i>n</i> = 14)	8.9	5.1	<0.31–48.1	0.31–5.0
UCD (<i>n</i> = 8)	4.2	4.3		
MCD (<i>n</i> = 6)	15.3	8.6		

MCD, multicentric CD; UCD, unicentric CD.

4 with a palpable mass and 4 were asymptomatic. In patients with unicentric CD (*n* = 17), the following presenting symptoms were found: eight with cough, six with pain, five with dyspnoea, five with haemoptysis and one with palpable mass. Two patients with unicentric CD were asymptomatic. In patients with MCD (*n* = 13), the following presenting symptoms were found: five with “B symptoms”, three with cough, three with dyspnoea, three with pain, three with palpable mass and two were asymptomatic.

B symptoms only occurred in patients with multicentric disease, two of which were multicentric NOS, two were HHV-8-associated multicentric and one was pure plasma-cell variant multicentric. One patient was HIV positive. Pleural fluid analysis in one patient revealed transudative lactate dehydrogenase (LDH) and protein ratios with a predominance of macrophages on cytology. Mean and median laboratory values for haemoglobin, haematocrit, CRP and IL-6 are presented in Table 1.

Imaging features of Castleman disease

CT

The mean and median size (maximum dimension) of the largest node across all patients was 5.4 and 4.5 cm, respectively. In unicentric CD, mean and median nodal size was 6.1 and 4.7 cm, respectively. In MCD, mean and median nodal size of the largest node was 4.5 and 4.1 cm, respectively. All nodes were well circumscribed on CT. 25 of 30 (83.3%) patients had nodes that were all uniformly homogeneous in appearance. In five patients, at least one node was heterogeneous. On non-contrast CT (*n* = 16), the nodes were hypodense to isodense to skeletal muscle, with a mean attenuation of 40.3 HU (range, 21–56 HU) and mean node to muscle attenuation ratio of 0.8 (range, 0.45–1.12 HU).

Calcification was seen in 8 (26.7%) cases, in the form of coarse calcifications (*n* = 5), punctate foci (*n* = 4) and arborizing (*n* = 1) (Figure 1). Of the eight nodes with calcification, five were in the setting of unicentric CD and three were in the setting

of MCD and were confined to one node. Of the calcified unicentric CD (*n* = 5), three were hyaline-vascular unicentric and two fell outside of the updated subtypes (“unicentric mixed” and “unicentric NOS”), with four occurring within the mediastinum and one within the retroperitoneum. Of the three cases of calcified multicentric disease, calcification was seen only at one nodal station. These multicentric cases had four, five and seven sites of lymphadenopathy; however, calcification was only seen within the middle mediastinum in each case.

Figure 1. A 40-year-old male with unicentric Castleman disease of an unidentified subtype, treated as hyaline-vascular variant. Non-contrast axial CT image demonstrates middle mediastinal nodal mass with “arborizing” (branching) (arrow) and punctate calcifications (arrowhead).

All cases that had contrast-enhanced CT scans available ($n = 26$) demonstrated nodal enhancement. The degree of enhancement was variable, with node-to-muscle attenuation ratios ranging from 1.1 to 4.2 (mean, 1.8; median, 1.7), as compared with skeletal muscle. All cases with pre- and post-contrast CT available ($n = 12$) exhibited greater post-contrast node-to-muscle attenuation ratios compared with pre-contrast, with mean and median pre-contrast ratio of 0.8 and 0.8 vs post-contrast ratio of 1.9 and 1.7, respectively. The hyaline-vascular variant had mean and median enhancement ratios of 1.6 and 1.6, respectively, compared with 2.1 and 1.9 for all other subtypes taken together. On contrast-enhanced CT ($n = 26$), the enhancement pattern was homogeneous in 21 of 26 (80.8%) patients and heterogeneous in 5 of 26 (19.2%).

In the cases of pleural effusion ($n = 3$), all were bilateral and small to moderate in size. There was no abnormal pleural thickening, nodularity or enhancement. One case (multicentric NOS) later developed lymphoma. The second case occurred in a patient with multicentric hyaline-vascular disease, with transudative fluid analysis. The third case occurred in a patient with known congestive heart failure (CHF) and had concurrent pulmonary oedema at the time of imaging. One patient with an effusion had trace ascites at presentation. No other patients had ascites at presentation.

Mean and median maximum spleen dimension as measured on CT was 10.8 and 10.4 cm, respectively. Mean and median maximum liver dimension as measured on CT was 22.3 and 22.4 cm, respectively.

Positron emission tomography

On PET ($n = 5$) at time of CD diagnosis, four cases were fluorine-18 fludeoxyglucose (^{18}F -FDG) avid. The four cases by subtype were: HHV-8-associated multicentric, plasma cell multicentric, hyaline-vascular multicentric and hyaline vascular unicentric. The one non- ^{18}F -FDG avid case was multicentric NOS. Of the ^{18}F -FDG-avid cases, nodal mean and median SUV_{max} were 4.7 and 4.3, respectively (range, 3.2–6.8). The mean and median number of ^{18}F -FDG-avid nodal stations was 6.75 and 8.00, respectively (range, 1–10). In one case of HHV-8-associated MCD, ^{18}F -FDG uptake in the spleen was greater than that in the liver, with a ratio of spleen to liver of 4.1/2.7. The cases that developed lymphoma did not have PET examinations at the time of CD diagnosis.

MR

On MRI ($n = 4$), all nodes were hypointense to isointense to muscle ($n = 2$ hypointense; $n = 2$ isointense) on T_1 weighted images. No lesions demonstrated T_1 shortening to suggest haemorrhage. On T_2 weighted images, nodes in three (75%) patients were hyperintense relative to muscle and one (25%) case was isointense to muscle. On post-gadolinium images, all cases ($n = 4$) demonstrated homogeneous enhancement. The enhancement pattern of these cases on CT was also homogeneous. Diffusion-weighted imaging (DWI) was not obtained.

Ultrasound

On ultrasound ($n = 3$), all nodes were hypoechoic, homogeneous and demonstrated posterior acoustic enhancement ($n = 3$,

hypoechoic; $n = 3$, homogeneous; $n = 3$, posterior acoustic enhancement) (Figure 2). Thin, barely perceptible internal echogenic septae were appreciated in two nodes. One node had internal flow with Doppler overlay; in the other two cases, no internal flow was detected upon Doppler interrogation (Figure 2).

Figure 2. A 25-year-old female with unicentric hyaline-vascular Castleman disease. (a) Greyscale ultrasound image of an enlarged peripancreatic node demonstrates a well-defined, hypoechoic lesion with posterior acoustic enhancement, with a few fine, hyperechoic internal septations. (b) Ultrasound image with colour Doppler overlay demonstrates the absent internal flow, simulating a “pseudo-cystic” appearance.

(a)

(b)

Lymphoma

Three patients developed three different types of non-Hodgkin's lymphoma: plasmablastic (Patient 1), diffuse large B-cell (Patient 2) and large cell (Patient 3). The median time of development of lymphoma from diagnosis of CD was 438 days (range, 282–960 days). All three cases that developed lymphoma were multicentric ($n = 3$). At the time of CD diagnosis, two of these patients presented with B-symptoms. The third patient developed B-symptoms in the interim before diagnosis of lymphoma. Two patients presented with splenomegaly, with splenic size >15 cm in both cases at presentation. The mean and median spleen size at the time of CD diagnosis in patients who went on to develop lymphoma was 13.9 and 15 cm, respectively, compared with 10.5 and 10.3 cm of those who did not.

At the time of CD diagnosis, mean and median maximum nodal dimension in patients who developed lymphoma ($n = 3$) were 3.3 and 3.0 cm, respectively. The first patient initially had an excisional axillary biopsy demonstrating HHV-8-associated (plasmablastic) MCD. New onset of haemolytic anaemia over a year after this excisional biopsy prompted clinical suspicion of lymphoma. Subsequent CT showed no change in the size of nodes or new sites of disease, although there was increased stranding surrounding lymph nodes. Repeat axillary excisional biopsy demonstrated plasmablastic lymphoma.

The second patient was originally diagnosed with hyaline-vascular variant of CD by excisional biopsy of mesenteric lymphadenopathy. Approximately, 9 months after this biopsy, the patient developed new B-symptoms. Subsequent CT

imaging revealed more confluent mesenteric and retroperitoneal lymphadenopathy, with an increase in maximal nodal dimension from 4.1 to 7.7 cm. The nodes also developed new heterogeneous enhancement and central low attenuation on CT (Figure 3). Subsequent core needle biopsy of the retroperitoneal lymphadenopathy demonstrated diffuse large-B cell lymphoma.

In the third patient, an initial diagnosis of CD was made by excisional biopsy of a cervical node demonstrating intermediate pathology, with both plasma cell and hyaline-vascular components. Nodal tissue tested negative for HHV-8, thus fitting into the classification of multicentric NOS. The abdomen was not imaged at the time of CD diagnosis. Prednisone was started for treatment of CD at the time of diagnosis. 2.6 years after initial diagnosis, an abdominal CT was performed owing to rising creatinine and revealed retroperitoneal adenopathy resulting in bilateral obstructive hydronephrosis. Subsequent fine-needle biopsy with flow cytometry demonstrated large cell lymphoma.

In two patients who developed lymphoma, one had a pleural effusion and one had pelvic ascites at the time of CD diagnosis. The patient with the pleural effusion developed pelvic ascites at the time of lymphoma diagnosis. The final patient developed a new pleural effusion and new pelvic ascites at the time of lymphoma diagnosis (Figure 3, Tables 2 and 3). In comparison, pleural effusion was seen in two patients with CD without development of lymphoma, one occurring in the setting of congestive heart failure.

Figure 3. A 70-year-old male with multicentric hyaline-vascular Castleman disease (CD), at the time of CD diagnosis. (a) Sagittal contrast-enhanced CT image demonstrates mesenteric adenopathy (arrow). (b) A 70-year-old male with multicentric hyaline-vascular CD, at the time of diagnosis of diffuse large B-cell lymphoma. (b) Sagittal contrast-enhanced CT image demonstrates increased confluent mesenteric adenopathy (solid arrow) and new pelvic ascites (dashed arrow).

Table 2. Features of patients who developed to lymphoma at time of Castleman disease (CD) diagnosis

Patient number	Age (years)	CD subtype	Spleen size (cm)	B symptoms	Number of sites	Maximum dimension (cm)	Calcification	Pleural effusion	Ascites	Time to lymphoma diagnosis (months)	Lymphoma type
Patient 1	36	Human herpesvirus 8 MCD	16.8	Yes	9	2.9	No	No	Trace	14.4	Plasmablastic
Patient 2	69	Hyaline-vascular MCD	15.0	No	2	4.1	No	No	No	9.3	Diffuse large B-cell
Patient 3	87	MCD not otherwise specified	10.0	Yes	3	3.0	Yes	Yes	No	31.5	Large cell

MCD, multicentric CD.

DISCUSSION

The imaging features of CD have been previously described in the literature but have been mainly limited to case reports, review articles and smaller retrospective reviews.^{9–11,13} The largest retrospective review to date consists of 34 patients with thoracic CD.¹⁴ There have been few other attempts to identify imaging features unique to the four updated subtypes of CD, based on combining the histopathology and distribution found at imaging.

The distribution of disease in our study, 17 (56.7%) unicentric and 13 (43.3%) multicentric, exhibits a higher proportion of multicentric disease than that described by other authors.¹⁵ This discrepancy may be owing to referral bias to a tertiary centre, as resected unicentric cases may be less likely to be referred as resection is typically curative. The hyaline-vascular variant accounted for 76% of unicentric disease, similar to previously published reports (76–91%).^{13,15,16} The hyaline-vascular variant occurred in a unicentric distribution in 78% of cases ($n = 14$) (multicentric in 22%), similar to a previously published report (74%),¹⁵ although lower than that quoted elsewhere in the radiology literature.^{8,10}

There has been a suggestion that heterogeneous enhancement is more common in lesions >5.0 cm.¹⁰ We found no association between the size of the lesion and enhancement pattern (homogeneous vs heterogeneous) or the degree of enhancement, although our evaluation was limited owing to our small sample size. No association between subtype and enhancement pattern was found.

We did not find that nodes in patients with hyaline-vascular variant enhanced more avidly than the other histological subtypes; this lack of avid enhancement differs from prior reports,^{8,13} although is similar to that found by Kwon et al.¹⁴ In fact, we found that the hyaline-vascular subtype had lower node-to-muscle attenuation ratios on contrast-enhanced CT than that of the other subtypes taken as a whole: mean and median enhancement ratios of 1.6 and 1.6 for hyaline vascular, compared with 2.1 and 1.9 for all other subtypes taken together. This may be owing, in part, to few patients with pure plasma-cell variant in our study population, which has been postulated to enhance less than hyaline vascular.¹³

Calcification has been reported in as many as 31% of cases of CD, with either a punctate, coarse or an “arborizing” (branching) pattern,⁹ with punctate being the most common.^{8,10,13} In our study, calcification was seen in 8 (26.7%) cases, in the form of coarse ($n = 5$), punctate foci ($n = 4$) and arborizing ($n = 1$) (Figure 1). The presence or absence of calcification did not significantly correlate with any specific subtype of CD.

There is a significant overlap in the clinical presentation and imaging features of CD and lymphoma, in particular, both often present with homogeneous multistation nodal involvement with variable enhancement. However, the presence of calcification seen in CD may help in differentiating CD from lymphoma, as calcification would be rare in untreated lymphoma. Notably, one patient with MCD-NOS with calcification eventually developed

Table 3. Features of untreated patients who developed lymphoma ($n = 2$) at the time of lymphoma diagnosis

Patient number	CD subtype	Spleen size (cm)	B symptoms	Number of sites	New sites	Maximum dimension (cm)	Pleural effusion	Ascites	Enhancement ratio	New central necrosis	New or increased nodal stranding
Patient 1	Human herpesvirus 8 MCD	18.9	Yes	9	No	2.9	Yes	Yes	2.2	No	Yes
Patient 2	Hyaline-vascular MCD	15.6	Yes	2	No	7.7	Yes	Yes	1.5	Yes	Yes
Patient 3	MCD not otherwise specified	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

CD, Castleman disease; MCD, multicentric CD; N/A, not applicable. Patient 3 was excluded as CD treatment was received in the interval.

lymphoma. Of the ^{18}F -FDG-avid cases ($n = 4$), nodal mean and median SUV_{max} were 4.7 and 4.3, respectively (range, 3.2–6.8), which overlap with that of low-grade lymphoma and are slightly less than that found by Lee *et al*¹⁷ (mean SUV_{max} , 5.8), who additionally found a significantly higher SUV_{max} in multicentric disease than in unicentric disease. Owing to small numbers, we were not able to demonstrate such a difference.

The appearance of CD on MR was consistent with prior reports. All nodes were hypointense to isointense to muscle on T_1 weighted images. On T_2 weighted images, nodes were hyperintense ($n = 3$) or isointense relative to muscle ($n = 1$). On post-gadolinium images, all cases ($n = 4$) demonstrated homogeneous enhancement. DWI was not obtained. Restricted diffusion in the case of a plasma cell variant has been described in the literature,¹⁸ but the potential utility of DWI in differentiating subtypes of CD is not currently known.

The appearance of CD on ultrasound also mimicked lymphoma, with posterior acoustic enhancement (enhanced through transmission) present in all cases ($n = 3$). The two cases not demonstrating internal Doppler flow were thought to be cystic until further imaging was obtained (Figure 2). This “pseudo-cystic” appearance is well known in lymphoma and speculated to be secondary to the homogeneous histology. This may explain the finding in our study, as all three cases were of the unicentric hyaline-vascular subtype.

We specifically looked at patients who developed lymphoma to determine if any features at diagnosis might raise suspicion of lymphoma. Patients with HHV-8-associated (plasmablastic) MCD are at known risk for developing plasmablastic lymphoma. Identifying patients outside of this subset is more challenging, although patients with multicentric disease and those experiencing B-symptoms may be at greater risk. Five patients had B-symptoms at the time of CD diagnosis, with two of these eventually developing lymphoma. The third patient with lymphoma developed B-symptoms at the time of lymphoma diagnosis. Clinical concern for lymphoma may be raised in patients with increasing adenopathy, a change in imaging appearance or new or worsening B-symptoms, and may warrant additional biopsy, as in the three cases that developed lymphoma of our cohort.

Two patients in this study who developed lymphoma had a spleen size ≥ 15.0 cm at the time of CD diagnosis. The mean and median spleen size at the time of CD diagnosis in patients who later developed lymphoma was 13.9 and 15.0 cm, respectively, compared with 10.5 and 10.3 cm of those who did not. This may suggest that splenic enlargement may be related to the development of lymphoma, although a larger subset of patients with lymphoma is clearly needed.

One of the two patients having no explanation for a pleural effusion eventually developed lymphoma. In the other two cases of lymphoma that received no treatment for CD, unilateral pleural effusion developed after the diagnosis of CD, accompanied by new small volume ascites in one case and unchanged trace ascites in the other case, just before the diagnosis of

lymphoma was made, raising the question that effusions and/or ascites may potentially herald the development of lymphoma.

We were able to classify 27 of 30 (90%) cases into the classification schemata as reviewed by Cronin and Warnke⁴ and did not find any imaging characteristics unique to a specific subtype. Three cases fell outside of the four subtypes. Two of these unclassified cases were unicentric in distribution by imaging and were of an intermediate (mixed) pathology, exhibiting features of both hyaline-vascular and plasma-cell variants. One of these two cases had no disease within the abdomen and pelvis on CT, although the neck was not imaged. The second case had only imaging of the thorax. Theoretically, such cases could represent MCD NOS, with subclinical disease at sites not imaged. However, this is felt to be unlikely in these cases given the absence of clinically palpable disease within the neck, and no symptoms at the unimaged sites. The other possibility is that this represents an additional subtype of CD—a unicentric mixed variant, which has been described by other authors.^{19,20} Cronin and Warnke allude to the “presence of hyaline-type follicles in some cases with a plasma cell component”, although do not distinguish this appearance as a distinct subtype.

A single case of unicentric disease falling outside the four subtypes exhibited histopathology “within the spectrum of CD”,

with “atypical features”, including a prominent meshwork of sclerosis and hyalinization in the interfollicular areas with dystrophic calcifications, and more B cells than were typically observed in the interfollicular zones. This patient was treated as having unicentric hyaline-vascular CD based on the aforementioned features, the absence of diagnostic features of malignancy on histopathology and the absence of a clonal lymphoid population on gene rearrangement studies. The significance of the atypical features seen in this case is unknown, although the descriptions of perivascular fibrosis and rare dystrophic calcification in hyaline-vascular CD have been described.¹⁹ This patient did not develop lymphoma.

The diagnosis of CD is made upon biopsy, with nodal distribution at imaging playing an important role in establishing unicentric vs multicentric disease, which, in turn, aids in establishing the subtype. The identification of imaging features unique to four subtypes remain elusive, although identifying features atypical for lymphoma, particularly calcification, is important. Additionally, we note that the patients in our study who developed lymphoma tended to have larger spleens and unexplained pleural effusions and/or ascites, raising a question of association between these findings and the development of lymphoma, although these observations clearly need validation with larger multicentre studies.

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