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Prevalence of Castleman's disease in patients suffering from cervical lymphadenopathy

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Abstract

Objectives: To determine the prevalence of Castleman's disease (unicentric/idiopathic multicentric CD) in a retrospective cohort according to the newly defined international diagnostic criteria in patients, who underwent a lymph node removal at a tertiary care university hospital over a period of 10 years.

Study design: Retrospective chart review.

Material and methods: All Patients with cervical lymphadenopathy coded by ICD-10-CM with "I88.9," "R59.0," or "D47.Z2" between January 2010 and December 2020 and who underwent a lymph node extirpation were identified. In cases who met the diagnostic criteria for a potential unicentric or idiopathic multicentric CD (iMCD) diagnosis, the lymph node tissue was re-evaluated by a pathologist.

Results: A total of 714 patients with cervical lymphadenopathy were included into this single-center retrospective study. After exclusion of patients with diseases that may mimic iMCD and cases for which material to perform histological re-evaluation was lacking, a subset of 75 patients with "nonspecific lymphadenitis" or "reactive hyperplasia of lymph node" was identified, who underwent a renewed histopathological examination. One case fulfilled both the major and minor criteria of an iMCD diagnosis, and further 15 cases matched the histological criterion of an iMCD diagnosis (one of the two major diagnostic criteria), so that a UCD diagnosis according to the new criteria could be accepted.

Conclusion: In this cohort, the subsequent application of the new diagnostic criteria led to further cases of CD (1.9% compared to 0.1% before) being recognized. Although incidence and prevalence of UCD and iMCD are low, clinicians should keep in mind this differential diagnosis as effective therapies are available.

Level of Evidence: 4.

KEYWORDS
cervical lymphadenopathy, head and neck, histopathology, idiopathic multicentric Castleman's disease, unicentric Castleman's disease

After being described first in 1956 by Benjamin Castleman, histopathological criteria for the diagnosis of Castleman's disease (CD) have been proposed from a solitary region of lymph nodes.[1] The initially described subtype of localized disease corresponds to the unicentric Castleman's disease (UCD). A second subtype has been proposed in the 1970s,[2] leading to the nowadays established differentiation between UCD and multicentric Castleman's disease (MCD).

Patients suffering of UCD typically present with localized benign hypertrophy of lymph nodes, infrequent B-symptoms, and no organ manifestation. Surgical resection is considered as standard therapy with high cure rates in UCD, and even radiotherapy seems to be a promising alternative.[3]

In contrast, MCD is a severe systemic disease, causing multilocular lymphadenopathy and affection of several organs, for example, hepatosplenomegaly. Symptoms are variable but acute episodes of physical weakness, fever, night sweats, and weight loss are frequent.[4] The etiology of MCD has not yet been fully understood. Evidently, there is an association with human immunodeficiency virus (HIV), but also the coinfection with human herpes virus 8 (HHV-8). The latter is postulated to encode a viral homolog of interleukin 6 (IL-6), a cytokine that is mainly in charge of the acute phase inflammatory reaction.[4] Not only in terms of a diagnostic but rather of therapeutic and prognostic issues the discrimination between HHV-8-positive and HHV-8-negative/idiopathic MCD (iMCD) is crucial. Rituximab-based treatments with/without concomitant chemotherapy have shown high remission rates in patients with HHV-8-MCD.[5] First line-treatments for iMCD consist of monoclonal antibodies like siltuximab (or tocilizumab, if siltuximab is not available) with/without corticosteroids, followed by the use of rituximab, immunomodulators, and chemotherapy in refractory patients.[6]

Because of the vast and often inconsistent spectrum of clinical symptoms, diagnosis of CD is made histologically using biopsy. However, due to extremely low incidence rates of 21–25 per million person-years,[7] the missing awareness for in both clinicians and histopathologists might lead to underestimated numbers of CD-diagnosis.[8]

An international expert meeting of Fajgenbaum et al. in 2017 defined new criteria, that is, specific symptoms and histopathological parameters for the diagnosis of iMCD.[9] The proposed grading system comprises five possible histopathologic features (A–E), which can be further characterized according to a grading scale of 0–3 (Table 1).[9] For the new histopathological subtype classification in iMCD, the historic "hyaline vascular" (HV) histopathologic MCD subtype was abandoned and replaced by a "hypervascular" (HyperV) subtype (Figure 1). This was to counteract confusion with HV features found in the recently described subset of iMCD patients with TAFRO syndrome.[9]

According to the new diagnostic concept, the diagnosis of iMCD requires two major criteria: a characteristic histopathology (Grade 2–3 for either regressed germinal centers (GCs) or plasmacytosis (PC) at minimum) and a certain number of affected lymph nodes (lymph nodes ≥1 cm enlarged in ≥2 lymph node stations). Minor criteria include clinical symptoms (e.g., B-symptoms, hypertrophy of spleen, and/or liver, edema) and laboratory values (e.g., CRP > 10 mg/L, anemia, thrombocytopenia).[9] As recently suggested in the consensus guidelines for the diagnosis and therapy of UCD developed following the iMCD consensus criteria, the spectrum of histopathological changes (A–E) seen in patients with UCD can be described and graded in a similar way. In UCD, however, the term "hyaline vascular" continues to apply for HV-UCD features (presence of regressed GCs and prominence of—often dysplastic—follicular dendritic cells, FDC), highlighting that the HV subtype is most commonly observed in UCD.[10] However, these guidelines do not provide a more precise definition of a minimum grading that is required for diagnostic classification as subtype HV-UCD, PC-UCD, or mixed UCD.

An estimation of CD prevalence for the German population does not exist yet. As lymphadenopathy often occurs primarily in the head and neck region, patients are frequently referred to the otorhinolaryngology department for further diagnostic workup including excisional biopsy and evaluation for possible differential diagnoses. The purpose of this retrospective study was to specify the proportion of CD diagnosis in a cohort of patients, who underwent a lymph node removal at a German center over a period of 10 years. Therefore, epidemiologic, laboratory and clinical data were analyzed descriptively although diagnosis of UCD and MCD was made on the basis of the international evidence-based consensus diagnostic criteria for iMCD proposed by Fajgenbaum et al. and the consensus diagnostic and treatment guidelines for UCD.[9,10]

1 | MATERIAL AND METHODS

This single-center retrospective study was carried out at the department of otolaryngology/head and neck surgery, university hospital of

TABLE 1 Histologic grading system of pathologic features in iMCD proposed by the new consensus diagnostic criteria for HHV-8-negative/iMCD (mod. After Fajgenbaum et al.[9])

Grade	Regressed GCs A	FDC prominence B	Vascularity C	Hyperplastic GCs D	PC E
0	No regressed GCs	No FDC prominence	Normal vascularity	No hyperplastic GCs	Normal PC
1	Few regressed GCs	Mild FDC prominence	Mildly increased vascularity	Few hyperplastic GCs	Mildly increased PC
2	Many regressed GCs	Moderate FDC prominence	Moderately increased vascularity	Many hyperplastic GCs	Moderately increased PC
3	Most GCs regressed	Very prominent FDCs	Very prominent vascularity	Most GCs hyperplastic	Very increased PC ("sheet-like")

the Technical University of Munich (TUM). We identified all patients with cervical lymphadenopathy coded between January 2010 and December 2020 by ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification) with "I88.9" ("nonspecific lymphadenitis, unspecified"), "R59.0" ("localized enlarged lymph nodes"), or "D47.Z2" ("Castleman disease"). Of the patients identified by ICD-10 codes, patients with malignancy, rheumatological diseases, evidence of infectious diseases (e.g. tuberculosis), and—as the largest group—with incomplete or missing histology were excluded. In most cases, only a punch biopsy was performed, which provided insufficient information. To evaluate for UCD and MCD according to the international consensus diagnostic criteria,[9] a manual chart review was carried out. Clinical data were collected from medical records including laboratory parameters (e.g., to exclude infectious causes), histological findings from the lymph node biopsy, and imaging findings (ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT)), and were analyzed on a descriptive basis. Patients were excluded if the lymphadenopathy was related to an active infection (i.e., caused by Epstein–Barr virus, HIV, and tuberculosis), an autoimmune disorder (i.e., systemic lupus erythematosus and rheumatoid arthritis) or malignant/lymphoproliferative disease (i.e., lymphoma and multiple myeloma) that can mimic iMCD. In cases that met the consensus criteria for a potential UCD or iMCD diagnosis, the lymph node tissue was re-evaluated histopathologically by a pathologist. The histological grading of pathologic features (Grade 0–3) and subtyping of iMCD into "hypervascular" (HyperV), "mixed" or "plasmacytic" was done as proposed by Fajgenbaum et al. (Table 1).[9] This study has been approved by the ethics committee of the Medical Faculty of TUM (No. 767/20 S -KK).
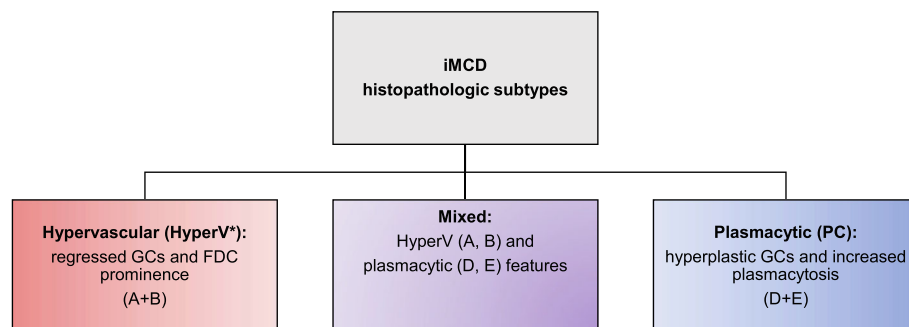
2 | RESULTS

2.1 | Reapplication of the newly defined diagnostic criteria

A total of 714 patients with cervical lymphadenopathy were included in this cohort. After excluding secondary diagnoses (patients with malignancy, rheumatological diseases, and evidence of infectious disease), and patients without histology, 336 patients had both

lymphadenopathy and lymph node extirpation. According to the in-house algorithm, patients with unspecific lymph node swelling received a treatment regimen with antibiotics, nonsteroidal anti-inflammatory agents, and a new sonographic assessment after 2 weeks; no lymph node extirpation was performed if the cervical lymphadenopathy regressed. After also excluding cases with incomplete or missing histology or cases for which material to perform histological re-evaluation was defective or lacking ($n = 261$), a subset of 75 patients with "nonspecific lymphadenitis" (ICD-10-CM diagnosis code I88.9) or "reactive hyperplasia of lymph node" (ICD-10-CM diagnosis code R59.9) was identified. These cases were subjected to a new histopathological evaluation. Sixteen of the 75 re-evaluated cases suggested CD due to CD-specific histopathological features in the lymph nodes. Two of the 16 potential CD patients had already initially been diagnosed with CD, one with an iMCD diagnosis and the other one with an UCD diagnosis.

For the remaining 14 patients, additional investigation was necessary to differentiate UCD, MCD, and iMCD diagnosis. All 14 patients had an imaging procedure before surgery, that is, at least sonography of the neck (all patients), additionally in almost all cases MRI ($n = 7$) or CT ($n = 2$) of the neck, or PET-CT ($n = 2$). Even if, retrospectively, it cannot be ruled out with absolute certainty that other lymph nodes were not pathologically enlarged, the available imaging/medical records suggest the presence of isolated cervical lymphadenopathy with a high degree of probability. However, initial documentation was evaluated for occurrence of minor criteria (laboratory and clinical symptoms) of iMCD diagnosis. None of the 14 cases had abnormal laboratory findings or fulfilled the clinical minor criteria of an iMCD diagnosis, which makes a UCD diagnosis most likely.

For a subsequent recording of clinical symptoms, which went beyond the available initial documentation, standardized questionnaires were developed and the patients were also explicitly asked via telephone about iMCD-specific symptoms (constitutional symptoms, large spleen and/or liver, fluid accumulation, eruptive cherry hemangiomatosis/violaceous papules, and lymphocytic interstitial pneumonitis). Eight out of 14 patients could be reached, with none of them met any of the five iMCD-related clinical symptom categories. None of the 14 patients had serologically or microbiologically abnormal findings that would have indicated an infection-related lymphoproliferative disorder. Even in the follow-up, these patients were not hospitalized again for any internal medicine concern. Hence, out of the

FIGURE 1 Three major histopathologic subtypes proposed by the new consensus diagnostic criteria for HHV-8-negative/iMCD (mod. According to Fajgenbaum et al.[9]). FDC, follicular dendritic cell; GCs, germinal centers.
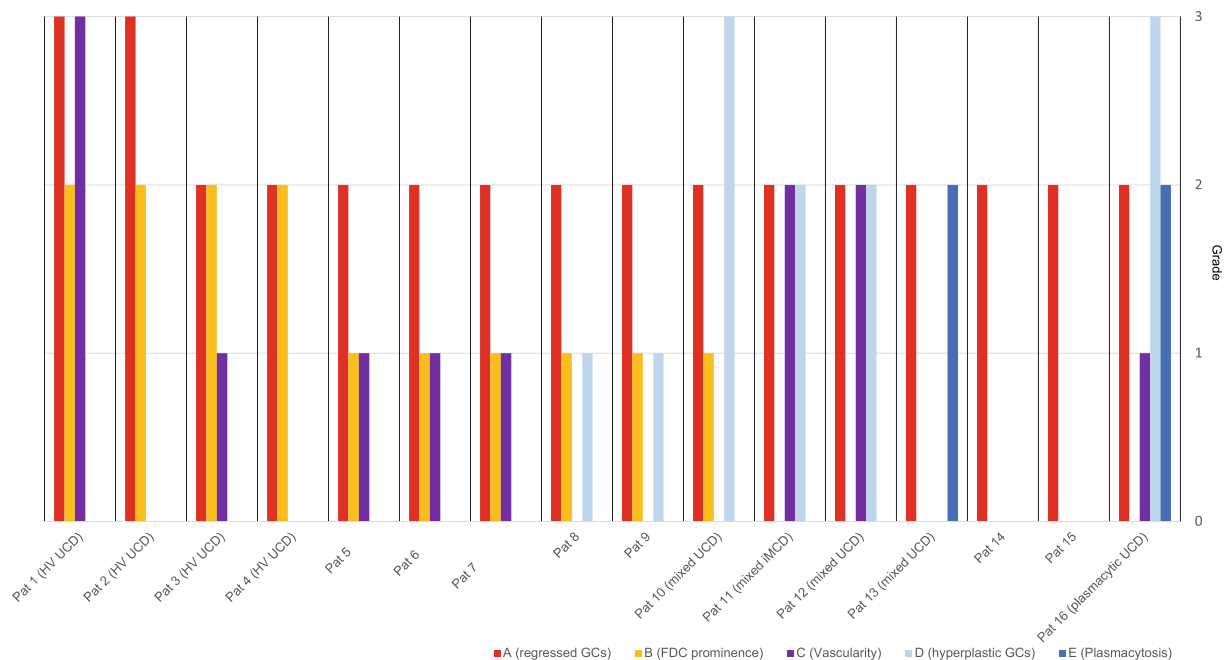
FIGURE 2 Distribution of histopathological changes seen in re-evaluated cases ($n = 16$) of our cohort according to the histopathological grading system.[9,10]

TABLE 2 Demographic data and patient characteristics of re-evaluated cases ($n = 16$)

	iMCD	UCD	All
n	1	15	16
Age	60 years		
Range			23–68 years
Mean		41 years	42 years
Median		38 years	38.5 years
Gender, n			
Male (%)	1 (6%)	8 (50%)	9 (56%)
Female (%)		7 (44%)	7 (44%)
Primary diagnosis	PC iMCD ($n = 1$)	Nonspecific lymphadenitis/reactive hyperplasia of lymph node ($n = 14$), UCD ($n = 1$)	
Diagnosis[a]/subtyping after re-evaluation	Mixed iMCD ($n = 1$)	HV UCD ($n = 4/8$; 50%)	Mixed iMCD (6%)
		PC UCD ($n = 1/8$; 12.5%)	HV UCD (25%)
			PC UCD (6%)
		Mixed UCD ($n = 3/8$; 37.5%)	Mixed UCD (19%)

Abbreviations: HV, hypervascular (formerly "hyaline-vascular" (HV) pathology)[9,10]; iMCD, idiopathic multicentric CD; PC, plasmacytic; UCD, unicentric Castleman's disease.
[a]Diagnostic criteria were initially developed for iMCD.[9]

75 histopathologically re-evaluated lymph nodes 16 CD patients were detected, with two initial diagnosis confirmed (1 iMCD/1 UCD), but 14 UCD cases newly diagnosed.

2.2 | Histopathology

Of the histopathologically re-evaluated UCD records, in all cases histopathological changes of category "A" (regressed GCs) or "E"

(PC) corresponding to at least Grade 2 (many regressed or hyperplastic GCs) were seen. In most cases, many regressed GCs (Grade 2) were present (Grade 2: $n = 14$; Grade 3: $n = 2$), four of which had a moderate FDC prominence ("B," Grade 2). In one of 14 cases (7%), a very prominent vascularity was also found ("C," Grade 3). Based on the grading system and proposed diagnostic criteria, which, however, refer to iMCD, four cases could be assigned to the HV subtype (no. 1–4, Figure 2). The histopathological features of three UCD patients corresponded to a mixed subtype (combination of HV and
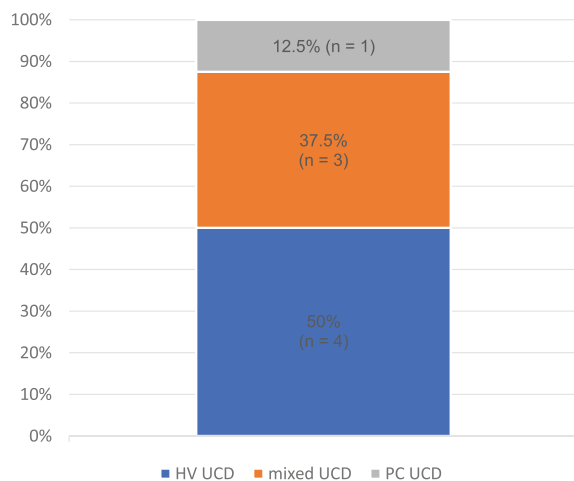
FIGURE 3 Distribution of pathologically recognized subtypes (UCD, $n = 8$). HV, hyaline-vascular[9,10]; PC, plasmacytic

plasmacytic features, no. 10, 12, 13; Figure 2). One UCD patient could be assigned to the PC subtype (no. 16, Figure 2). In two cases, no further changes in accordance with the proposed histopathological categories "A–E" could be detected histopathologically except for regressed GCs (no. 14, 15; Figure 2). The patient who fulfilled both the major and minor criteria of an iMCD diagnosis, HyperV and plasmacytic features seemed most likely to be assigned to a mixed iMCD (no. 11, Figure 2).

2.3 | Patient demographics

Of the 16 cases re-evaluated, 9 were male and 7 were female. The average age was 42 years (range: 23–68 years). Based on the cases that were histopathologically assigned to a certain subtype ($n = 8$), the proportion of patients with HV UCD was 50% (4/8), with mixed UCD 37.5% (3/8), and with PC UCD ($n = 1$) 12.5%. Demographic and histopathological patient characteristics are summarized in Table 2 and Figure 3.

3 | DISCUSSION

In this single-center retrospective analysis of the medical records of 714 patients with cervical lymphadenopathy over a period of 10 years, 14 cases of a UCD were newly recorded (1.9%), which at least fulfilled the histological criterion of the new diagnostic criteria tailored to iMCD.[9] Histopathological subtype classification was carried out in eight cases – according to the proposed newer consensus diagnostic criteria.[9,10] The percentage of patients with UCD and HV histopathology is reported in the literature as 70%–90%.[11,12] With 50%, the HV subtype was also the most common (4/8) in our analysis. However, the proportion would have been even higher if the newer grading system were not applied to the UCD cases. Because the histopathological changes used to characterize the CD variants cover a broad spectrum and cannot be clearly assigned

to a group in every case,[11] the new consensus criteria define the presence of regressive GCs and FDCs—as the hypervascular (or hyaline-vascular, HV) end of the spectrum—and prominent hyperplastic GCs and PC as the other end with at least Grade 2–3 for either regressive GCs or PC).[9–11] After applying these minimum grading requirements to the UCD cases, only four of the newly added UCD pathologies could still be graded as HV subtypes. Seven cases (44%) had a grading of two only for the pathological feature "regressed GCs" (A). All other four features achieved a grading of 1 at best, so that for these cases no clear assignment of the histological subtype could be made (Figure 2). With a less strict handling of the histopathological grading, it can be discussed whether these seven UCD cases could also be assigned to the HV subtype, which would result in a total HV rate of 69%. The estimated proportion of UCD patients with PC histopathology is between 10% and 20% according to the literature,[10] which would also fit the 12.5% in our analysis. A similar result (68% HV UCD, PC, or mixed UCD in 32%) was also obtained by a French working group that studied a UCD cohort of 57 patients.[13]

However, neither the reliability nor the clinical usefulness of a subtyping into HyperV/HV, PC or mixed CD has yet been clarified; especially, because transitions between the variants can also take place (as seen in subsequent biopsies), or several subtypes can occur at different sites within the same patient.[9] According to this, histopathology is suitable for diagnosing CD at all, but cannot be used as the sole determinant for the clinical patient management.[11]

Epidemiological data on CD are generally scarce,[11] and as a rare disease CD has been granted orphan status. In a systematic review of published data, iMCD accounted for at least 33% of all published cases of MCD.[6] This would correspond to approximately five cases per 1 million patient-years. The 10-year prevalence of MCD has been estimated to be 2.3 per million adults in the catchment area of the Fred Hutchinson Cancer Research Center, Seattle WA, USA.[14]

Using a commercial claims database, the incidence for CD in the United States was calculated as 21–25 per million person-years, with 23% of CD patients suffering from MCD. There is no final consensus on the proportion of UCD versus MCD. However, assuming that MCD occurs in 23% of potential patients with CD, the incidence of MCD and UCD was estimated to be 5.1 and 15.9 cases per million person-years, respectively. According to the study authors, this translated (based on the US population in 2010) to an annual incidence of 1569 patients with MCD and 4932 patients with UCD.[7] A more recent analysis published in early 2022 using an administrative US claims database found an annual incidence of 1213 total MCD cases, 800 UCD cases, and 1022 iMCD cases for 2018. The incidence of MCD, UCD, and iMCD was estimated to be 3.7, 2.5, and 3.1 cases per million individuals, respectively.[15] In this study, the evidence-based consensus diagnostic criteria for HHV-8-negative/iMCD[9] were also applied, according to which the diagnostic or laboratory claims for ≥2 minor criteria had to be fulfilled to diagnose iMCD. All patients with <2 minor criteria were defined as having UCD.[15] This would correspond to about 160–240 new iMCD cases per year in Germany, although it is not possible to make more precise estimates due to the inconsistencies in the diagnostic criteria used to date.

The gender distribution in the UCD patients was comparable (44% female and 56% male), which also corresponds to the data from

the literature.[11,16] With a broad range (diagnosis possible at almost any age), the third to fourth decade of life is considered the most common age of UCD onset.[10,11,17] In our cohort, the median age of the patients was also 38 years. The diagnosis of iMCD is also associated with a wide age range, but usually manifests at the fifth to sixth decade[9,11] (60 years at the time of biopsy in our cohort, $n = 1$). However, there are no known epidemiological factors that predispose to UCD development.[10] Even though iMCD-like symptoms (such as constitutional symptoms according to the minor clinical iMCD criteria) are described more frequently in patients with PC UCD or mixed UCD,[10] we could not detect any comparable clinical symptoms, any other more serious complications (such as polyneuropathy, pulmonary complications, or autoimmune hemolytic anemia), or any laboratory abnormalities. The observation that the vast majority of patients with UCD appear to be asymptomatic is also consistent with the findings of the French cohort.[13] However, because the prognosis of MCD is relatively unfavorable,[4] pathologists and clinicians should always consider the presence of a multicentric CD as a differential diagnosis to facilitate a prompt recognition.

One of the significant limitations of this study is related to its retrospective nature. In addition, the patient cohort was limited to a single center, so the sample size was limited. As this is a maximum care hospital, patients with CD may be over-represented in our data set.

4 | CONCLUSION

The subsequent application of the new diagnostic criteria increased the percentage of detected CD patients to 1.9%, compared to 0.1% before (with iMCD and UCD, respectively). In the case of the already known iMCD patient, the histopathological re-evaluation with the newer grading system led to a different subtype. Thus, the proportion of patients with CD in this cohort could be specified retrospectively, albeit a description of the prevalence due to the lack of reference to a representative proportion of the total population.

The results of our study indicate that the implementation of the new diagnostic criteria could help to identify UCD cases more easily and, if necessary, to adjust the required further diagnostic procedure. Because cervical regions are one of the most common sites of UCD manifestation,[11,13] with the neck accounting for 23%,[10] this rare diagnosis should also be considered in the differential diagnosis of patients with nonspecific lymphadenopathy. The distinction between UCD and MCD also has therapeutic and prognostic consequences for the individual patient; because it requires different treatment approaches. For further refinement of the diagnostic criteria, the establishment of a national patient registry and the initiation of prospective multicenter studies should be endorsed.

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REFERENCES
1. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph-node hyperplasia resembling thymoma. *Cancer*. 1956;9(4):822-830.
2. Gaba AR, Stein RS, Sweet DL, Variakojis D. Multicentric giant lymph node hyperplasia. *Am J Clin Pathol*. 1978;69(1):86-90.
3. Chronowski GM, Ha CS, Wilder RB, Cabanillas F, Manning J, Cox JD. Treatment of unicentric and multicentric Castleman disease and the role of radiotherapy. *Cancer*. 2001;92(3):670-676.
4. Waterston A, Bower M. Fifty years of multicentric Castleman's disease. *Acta Oncol*. 2004;43(8):698-704.
5. Lurain K, Yarchoan R, Uldrick TS. Treatment of Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Hematol Oncol Clin North Am*. 2018;32(1):75-88.
6. van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. *Blood*. 2018;13(20):2115-2124.
7. Munshi N, Mehra M, van de Velde H, Desai A, Potluri R, Vermeulen J. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. *Leuk Lymphoma*. 2015;56(5):1252-1260.
8. Hoffmann C, Tiemann M. Multizentrischer Morbus Castleman: Selten korrekt diagnostiziert. *Dtsch Arztebl*. 2019;116(46):32.
9. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood*. 2017;129(12):1646-1657.
10. van Rhee F, Oksenhendler E, Srkalovic G, et al. International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease. *Blood Adv*. 2020;4(23):6039-6050.
11. Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. *Blood*. 2020;135(16):1353-1364.
12. Saeed-Abdul-Rahman I, Al-Amri AM. Castleman disease. *Korean J Hematol*. 2012;47(3):163-177.
13. Oksenhendler E, Boutboul D, Fajgenbaum D, et al. The full spectrum of Castleman disease: 273 patients studied over 20 years. *Br J Haematol*. 2018;180(2):206-216.
14. Robinson D, Reynolds M, Casper C, et al. Clinical epidemiology and treatment patterns of patients with multicentric Castleman disease: results from two US treatment centres. *Br J Haematol*. 2014;165(1):39-48.
15. Mukherjee S, Martin R, Sande B, Paige JS, Fajgenbaum DC. Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6-directed therapy. *Blood Adv*. 2022;6(2):359-367.
16. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. *Br J Haematol*. 2005;129(1):3-17.
17. Talat N, Schulte KM. Castleman's disease: systematic analysis of 416 patients from the literature. *Oncologist*. 2011;16(9):1316-1324.