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ORIGINAL PAPER

Haematological Malignancy - Clinical

The application of a multidisciplinary approach in the diagnosis of Castleman disease and Castleman-like lymphadenopathies: A 20-year retrospective analysis of clinical and pathological features

Sabrina Pelliccia[1] | **Evelina Rogges**[2] | **Antonello Cardoni**[3] | **Gianluca Lopez**[2] | **Esmeralda Conte**[1] | **Anna Laura Faccini**[1] | **Rita De Vito**[3] | **Katia Girardi**[4] | **Antonella Bianchi**[5] | **Ombretta Annibali**[6] | **Stefano Fratoni**[7] | **Daniele Remotti**[8] | **Gioia De Angelis**[9] | **Carla Giordano**[10] | **Giovanna Palumbo**[11] | **Stefania Scarpino**[2] | **Flavia Del Porto**[12] | **Maria Paola Bianchi**[1] | **Francesca Di Gregorio**[13] | **Agostino Tafuri**[1] | **Arianna Di Napoli**[2]

[1]Haematology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza University, Rome, Italy

[2]Pathology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza University, Rome, Italy

[3]Pathology Unit, IRCCS Bambino Gesù Children's Hospital, Rome, Italy

[4]Department of Pediatric Hematology and Oncology and Cell and Gene Therapy, IRCCS Bambino Gesù Children's Hospital, Rome, Italy

[5]Pathology Unit, Campus Bio-Medico University Hospital, Rome, Italy

[6]Haematology Stem Cell Transplantation Unit, Campus Biomedico University Hospital, Campus Bio Medico University, Rome, Italy

[7]Surgical Pathology Department, Sant' Eugenio Hospital, Rome, Italy

[8]Pathology Unit, Belcolle Hospital, Viterbo, Italy

[9]Haematology Unit, Belcolle Hospital, Viterbo, Italy

[10]Department of Translational and Precision Medicine, A.O.U. Policlinico Umberto I, Sapienza University, Rome, Italy

[11]Haematology Unit, Department of Translational and Precision Medicine, A.O.U Policlinico Umberto I, Sapienza University, Rome, Italy

[12]Internal Medicine Unit, Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza University, Rome, Italy

[13]Radiology Unit, Department of Surgical-Medical Sciences and Translational Medicine, Sant'Andrea University Hospital, Sapienza University, Rome, Italy

Correspondence
Arianna Di Napoli, Pathology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza University, Rome, Italy.
Email: arianna.dinapoli@uniroma1.it

Summary

Background: Castleman disease (CD) comprises a group of rare and heterogeneous haematological disorders, including unicentric (UCD) and multicentric (MCD) forms, the latter further subdivided into HHV8-MCD, POEMS-MCD and idiopathic-MCD (iMCD). However, according to the Castleman Disease Collaborative Network guidelines, the diagnosis of CD can only be achieved through collaboration between clinicians and pathologists.

Methods: We applied these clinical and pathological criteria and implement with clonality testing to a retrospective cohort of 48 adult and paediatric Italian patients diagnosed with reactive lymphadenitis with CD-like histological features.

Results: We confirmed the diagnosis of CD in 60% (29/48) of the cases, including 12 (41%) UCD and 17 (59%; five HHV8-MCD, three POEMS-MCD and nine iMCD) MCD. Of the remaining 19 cases (40%) with multiple lymphadenopathy, 5 (26%) were classified as autoimmune diseases, 1 (5%) as autoimmune lymphoproliferative

Sabrina Pelliccia and Evelina Rogges contributed equally to this work.

disorder, 1 (5%) as IgG4-related disease, 11 (83%) as reactive lymphadenitis and 1 (5%) as nodal marginal zone lymphoma.

Conclusions: Our study emphasizes the importance of the multidisciplinary approach to reactive lymphadenitis with CD-like features in order to achieve a definitive diagnosis and choose the appropriate treatment.

KEYWORDS

ALPS, autoimmune lymphadenitis, Castleman disease, IgG4

INTRODUCTION

Castleman disease (CD), first described in 1954[1] as an enlarged mediastinal lymph node, now encompasses a group of rare and heterogeneous haematological disorders that share a spectrum of lymph node histopathology as well as a wide range of clinical features related to systemic inflammation, cytopenias and life-threatening multiple organ dysfunction.[2–5]

Great progress has been made in diagnosing and managing this disease since the publication of the Castleman Disease Collaborative Network (CDCN) guidelines for diagnosis and treatment.[6–9] Based on these clinical and pathological criteria, CD is classified as unicentric (UCD) if a single lymph node or several lymph nodes in the same region are affected and multicentric (MCD) when multiple lymph node stations are involved. MCD is then further divided into MCD associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, clonal plasma cell disorder and cutaneous lesions), MCD associated with human herpes virus 8 (HHV8) infection and idiopathic-MCD (iMCD), the latter further divided into iMCD associated with TAFRO syndrome (thrombocytopenia, ascites, bone marrow reticulin fibrosis, renal dysfunction and organomegaly) and iMCD not otherwise specified. Histologically, CD has been classified as hyaline-vascular type (HV-CD), plasma cell type (P-CD) and mixed type (mixed-CD) based on the aspect of the lymphoid follicles (regressed or hyperplastic) and the degree of interfollicular plasmacytosis and vascularity. UCD shows more frequently HV-CD histology, whereas P-CD and mixed-CD are more frequently multicentric.[9]

Patients with UCD are often asymptomatic and present with an enlarged lymph node (median diameter 5 cm), more frequently in the mediastinum, neck or abdomen, incidentally found during imaging exams for unrelated problems or because of signs of compression of vital structures. Complete surgical excision of the mass is almost always curative.[8] A clonal expansion of stromal cells has been proposed as a pathogenetic event.[10–13] Conversely, the aetiology of MCD is unknown, with several suggested mechanisms sharing an excessive production of interleukin-6 (IL-6) and vascular endothelial growth factor.[6] Recently, the dysregulation of the signalling IL-6-JAK-STAT3 and PI3K/Akt/mTOR has been identified as implicated in iMCD pathogenesis and can represent alternative therapeutic targets in IL-6 blockade–refractory iMCD.[14–16] Patients with MCD have more than one enlarged lymph node (>1 cm in size) and may exhibit a wide spectrum of clinical manifestations (i.e. fever, weight loss, fatigue, night sweats, fluid accumulation) and laboratory abnormalities (anaemia, thrombocytopenia/thrombocytosis, increased ESR and CRP, polyclonal hypergammaglobulinaemia, hypoalbuminaemia and renal dysfunction) that may go into remissions and exacerbations, thus requiring systemic treatments using anti-IL-6 therapy (i.e siltuximab) or rituximab.[17,18] The diagnosis of HHV8-MCD requires the presence of HHV8 infection by both serology and immunohistochemistry, while neurological evaluation and electrophoresis with serum and urine immunofixation are essential to diagnose POEMS-MCD. The exclusion of various autoimmune, malignant and infectious diseases (i.e. IgG4-related disease [IgG4-RD], rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], autoimmune lymphoproliferative disorder (ALPS), HIV-related lymphadenopathy, and Hodgkin and non-Hodgkin lymphomas) is mandatory for iMCD diagnosis, as CD-like features could also be found in non-CD lymphadenopathy.[19–21]

According to these CDCN diagnostic criteria, a comprehensive multidisciplinary approach is required to diagnose CD. We retrospectively reviewed 49 reactive lymphadenitis with 'Castleman-like' histopathological features by integrating histological, molecular, clinical, serological and imaging findings in order to better classify the lymphadenopathy as CD or non-CD.

PATIENTS AND METHODS

Case selection

Thirty-seven patients diagnosed with reactive lymphadenopathy with histological features resembling CD at Sant'Andrea University Hospital of Rome, Italy, were enrolled in the study from 2003 to 2022. Additional 11 cases diagnosed in other Italian hospitals (Campus Biomedico, Policlinico Umberto I, Sant'Eugenio Hospital, Belcolle Hospital and Bambino Gesu' Hospital) belonging to the haematopathology study group of Lazio region were included. Informed consent was obtained from the patients, and the study was performed in accordance with the Declaration of Helsinki.

Clinical, laboratory and imaging data collection

Patients' data (age and gender), clinical history (symptoms, signs and concomitant diseases), radiological

findings (involved lymph node stations, hepatomegaly and/or splenomegaly), laboratory results (blood count, erythrocyte sedimentation rate, albumin levels, protein electrophoresis and renal function tests) and virological status (HIV, Epstein–Barr virus [EBV] and HHV8) were retrospectively collected. We also investigated the presence of autoimmune diseases, lymphoproliferative disorders and other neoplastic conditions. Follow-up data are available up to 2023.

Histological review

Three different pathologists (ADN, AC, ER) conducted a histological review of each case according to CDCN criteria.[6,8] Immunohistochemical stainings for LANA1 (Clone 13B10, Gennova, Sevilla, Spain), IgG (Polyclonal Rabbit, DAKO, Agilent Santa Clara, CA, USA), IgG4 (Clone EP4420, GeneTex, Irvine, CA, USA) and LMP1 (Clone CS.1-4, DAKO, Agilent) were performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections, using an automated immunostainer (OMNIS, Agilent). The number of IgG4-positive plasma cells and the IgG4/IgG ratio were also evaluated according to the consensus statement on the pathology of IgG4-RD.[21] In situ, hybridization for EBV was also performed using Epstein–Barr Virus (EBER) PNA Probe/Fluorescein and FITC/HRP (DAKO, Agilent).

Clonality analyses

Immunoglobulin heavy chain (IGH), T-cell receptor gamma (TRG) and T-cell receptor β (TRB) gene rearrangements were evaluated on DNA extracted from FFPE tissue samples (QIAamp Mini Kit (Qiagen, Hilden, Germany) by the gene scan PCR approach (IdentiClone, InVivoScribe Technologies, San Diego, CA, USA) as previously described.[22,23] In an HHV8-MCD, IGH clonality testing was repeated on follicles and interfollicular areas laser microdissected from FFPE tissue sections (Laser Micro dissector SL CUT, Nikon Instruments, New York, NY, USA).

Diagnostic criteria

CDCN guidelines[6–8] detailed in Table 1 have been applied for UCD and MCD diagnosis. Lymph nodes consistent with CD were defined as HHV8-MCD by a positive immunostaining against the HHV8 latent nuclear antigen (LANA-1). POEMS-MCD were diagnosed when both mandatory criteria: polyradiculoneuropathy and monoclonal plasma cell-proliferative disorder; one of the three major criteria: lymph nodes consistent with CD, sclerotic bone lesions and high VEGF; and one of the six minor criteria: organomegaly, extravascular fluid accumulation, endocrinopathy, papilledema, thrombocytosis/polycythaemia and skin changes (hyperpigmentation, hypertrichosis, glomeruloid haemangiomata, plethora, acrocyanosis, flushing and white nails) for POEMS were present.[2,9]

RESULTS

Classification of lymphadenopathies

The clinicopathological review of the 48 patients enrolled with a diagnosis of reactive lymphadenitis with CD-like histology confirmed the diagnosis of CD in 29/48 cases (60%). In particular, 12 cases (25%) involving a single lymph node station were all confirmed as UCD (Table 2), while of the 36 patients with multiple enlarged lymph nodes (Table 3), 17 cases (35%) were diagnosed as MCD (5 HHV8-MCD [29%], 3 POEMS-MCD [18%] and 9 iMCD [53%]). Of the remaining 19 cases (40%), 5 (26%) were classified as autoimmune diseases, 1 (5%) as ALPS, 1 (5%) as IgG4-RD, 10 (53%) as reactive lymphadenitis, 1 (5%) as reactive lymphadenitis associated with HIV infection and 1 (5%) as nodal marginal zone lymphoma (NMZL) with CD-like features.

Clinicopathological features of UCD

All UCD cases (12 cases) involved 10 adult patients (seven females and three males, median age 39 years, range 30–77) and two paediatric patients (all males, median age 13.5 years, range 12–15). The most involved lymph nodes were mediastinal (four cases), supraclavicular (three cases) and later cervical (two cases), with a diameter ranging from 1.1 to 7.5 cm (mean 4 cm). Clinically, none of these patients had symptoms or relevant laboratory alterations. All patients were in complete remission after surgery. The histological pattern was HV-CD in 10 cases and mixed-CD in two cases. HHV8 was negative in all patients. There was a significant increase in the intrafollicular IgG4+ plasma cells and an IgG4/IgG ratio >40% only in one case (Case 11). However, the patient's IgG4 serum level was normal, excluding IgG4-RD. Monoclonal IGH rearrangement was found in only one case (Case 1). This was characterized by a large mediastinal mass with dysplastic follicular dendritic cells (FDCs) and a small IgM kappa-monotypic interstitial plasmacytosis (Figure 1). Patients had a small IgM kappa serum paraprotein (0.5 g/dL) and a minimal bone marrow infiltration (5% of total cellularity) of kappa-restricted plasma cells consistent with a monoclonal gammopathy of undetermined significance (MGUS). In addition, an identical monoclonal IGH rearrangement was documented in the lymph node and the bone marrow blood (Figure 1E). In another UCD case (Case 8), the presence of a conspicuous T-lymphoblastic population (TDT+, CD3+/−, CD7+, CD99+, CD5+/−, CD4+, CD8+, CD1A+, LMO2-) was found in association with the HV-CD histological features. The absence of cytokeratin-positive cells and the evidence of polyclonal rearrangements of both TRG and TRB genes led us to consider this population as an indolent T-lymphoblastic proliferation within the UCD (Figure 2).

TABLE 1 CDCN guidelines for CD diagnosis (adapted from Fajgenbaum et al.[6]).

I. Major Criteria (need both)
1. Histopathologic lymph node features consistent with the CD spectrum (need grade 2–3 for either regressive GCs or plasmacytosis at minimum)
Regressed/atrophic/atretic germinal centers, often with expanded mantle zones composed of concentric rings of lymphocytes in an "onion skinning" appearance (grade 0–3)
FDC prominence (grade 0–3)
Vascularity, often with prominent endothelium in the interfollicular space and vessels penetrating into the GCs with a "lollipop" appearance (grade 0–3)
Sheetlike, polytypic plasmacytosis in the interfollicular space (grade 0–3)
Hyperplastic GCs (grade 0–3)
2. Enlarged lymph nodes (≥1 cm in short-axis diameter)
In a single lymph node station/region for UCD
In ≥2 lymph node stations for MCD
II. Minor Criteria for iMCD (need at least 2 of 11 criteria with at least 1 laboratory criterion)
Laboratory
1. Elevated CRP (>10 mg/L) or ESR (>15 mm/h)
2. Anemia (hemoglobin <12.5 g/dL for males, hemoglobin <11.5 g/dL for females)
3. Thrombocytopenia (platelet count <150 k/μL) or thrombocytosis (platelet count >400 k/μL)
4. Hypoalbuminemia (albumin <3.5 g/dL)
5. Renal dysfunction (eGFR <60 mL/min/1.73 m^2) or proteinuria (total protein 150 mg/24 h or 10 mg/100 mL)
6. Polyclonal hypergammaglobulinaemia (total γ globulin or immunoglobulin G > 1700 mg/dL)
Clinical
1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (≥2 CTCAE lymphoma score for B-symptoms)
2. Large spleen and/or liver
3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion
4. Eruptive cherry hemangiomatosis or violaceous papules
5. Lymphocytic interstitial pneumonitis
III. Exclusion Criteria (must rule out each of these diseases that can mimic CD)
Infection-related disorders
1. HHV-8 (infection can be documented by blood PCR, diagnosis of HHV-8–associated MCD requires positive LANA-1 staining by IHC, which excludes iMCD)
2. Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (detectable EBV viral load not necessarily exclusionary)
3. Inflammation and adenopathy caused by other uncontrolled infections (e.g. acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis)
Autoimmune/autoinflammatory diseases (requires full clinical criteria, detection of autoimmune antibodies alone is not exclusionary)
1. Systemic lupus erythematosus
2. Rheumatoid arthritis
3. Adult-onset Still disease
4. Juvenile idiopathic arthritis
5. Autoimmune lymphoproliferative syndrome
Malignant/lymphoproliferative disorders (these disorders must be diagnosed before or at the same time as iMCD to be exclusionary)
1. Lymphoma (Hodgkin and non-Hodgkin)
2. Multiple myeloma
3. Primary lymph node plasmacytoma
4. FDC sarcoma
5. POEMS syndrome
Select additional features supportive of, but not required for diagnosis
Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M
Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
Diagnosis of disorders that have been associated with iMCD: paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (without diagnosing POEMS), glomerular nephropathy, inflammatory myofibroblastic tumor

Clinicopathological features of HHV8-MCD

The five patients with HHV8-MCD (Table 3) were three males and two females, with a median age of 72.4 years (range 53–83). The disease involved multiple supra- and infra-diaphragmatic, retropectoral, bilateral axillary, lumbo-aortic, iliac and inguinal lymph nodes with a diameter ranging from 2 to 5 cm. All patients were negative for HIV infection, and only one died within 30 months (range 1–96) after diagnosis. The histological pattern was mixed type in four cases and plasma cell type in one case, with HHV8-positive plasmablasts in the follicular mantle zones in all the cases. The number of IgG4 plasma cells was not increased. Interestingly, a monoclonal IGH rearrangement within a polyclonal background was detected in one case (Case 17). The patient was an 82-year-old man with multiple lymphadenopathy and elevated acute-phase inflammatory serum proteins. The cervical lymph node showed mixed-CD with HHV8+, IgM+ lambda+ plasmablasts sparse in the follicular mantle zones. The interfollicular areas were populated with numerous IgG+ polytypic plasma cells and scattered EBER-positive/LMP1-negative lymphocytes (Figure 3). Clonality analysis repeated on microdissected follicles and interfollicular areas confirmed the presence of the monoclonal IGH rearrangement only in the interfollicular areas. This finding ruled out the possibility of an incipient HHV8-positive large B-cell lymphoma but did not exclude the possibility of an incipient interfollicular monoclonal B-cell proliferation.

TABLE 2 Clinicopathological characteristics of 12 UCD.

Case ID	Age/sex	Site	Size (cm)	Diagnosis	Regressed GC[a]	FDC hyperplasia[a]	Vasculature[a]	Hyperplastic CG[a]	Plasmacytosis[a]	HHV8	IgG4 plasma cells	IgG4/IgG ratio	IGH clonality	Follow-up
1	56/F	Mediastinal	7.5	UCD mixed type	3	3 (with dysplasia)	3	0	2 (kappa-restricted)	Negative	<100/HPF	<40%	Biallelic/ Biclonal	Complete remission
2	15/M	Iliac	5	UCD HV type	3	3	2	0	0	Negative	n.v.	n.v.	Polyclonal	Complete remission
3	12/M	Cervical	3	UCD HV type	3	3 (with dysplasia)	2	1	0	Negative	<100/HPF	<40%	Polyclonal	Complete remission
4	42/F	Axillary	5	UCD HV type	2	1	3	2	1	Negative	<100/HPF	<40%	Polyclonal	Complete remission
5	55/M	Mediastinal	2	UCD HV type	2	2	2	1	0	Negative	<100/HPF	<40%	Polyclonal	Complete remission
6	57/F	Pleural	2.1	UCD HV type	2	2	3	1	0	Negative	<100/HPF	<40%	Polyclonal	Complete remission
7	40/F	Mediastinal	5	UCD HV type	3	3	2	1	0	Negative	<100/HPF	<40%	Polyclonal	Complete remission
8	42/F	Mediastinal	5	UCD mixed type (with lymphoblasts)	3	2	2	0	2	Negative	<100/HPF	<40%	Polyclonal	Complete remission
9	30/M	Sovraclavear	5	UCD HV type	3	2	3	1	1	Negative	<100/HPF	<40%	Polyclonal	Complete remission
10	31/M	Cervical	4	UCD HV type	3	2	2	0	1	Negative	n.v.	n.v.	Polyclonal	Complete remission
11	49/F	Sovraclavear	3.5	UCD HV type	3	3	3	0	1	Negative	>100/HPF	>40% (serum IgG4 within normal range)	Polyclonal	Complete remission
12	77/F	Sovraclavear	1.1	UCD HV type	2	2	1	0	1	Negative	<100/HPF	<40%	Polyclonal	Complete remission

[a]A score from 0 to 3 was assigned as reported by van Rhee et al.[8]

TABLE 3 Clinicopathological characteristics of 17 MCD.

Case ID	Age/sex	Involved lymph nodes	Biopsy site (size)	Diagnosis	Regressed GC[a]	FDC hyperplasia[a]	Vasculature[a]	Hyperplastic CG[a]	Plasmacytosis[a]	HHV8	IgG4 plasma cells	IgG4/IgG ratio	IGH clonality	Laboratory criteria	Clinical criteria	Treatment and follow-up
13	53/F	Retro-pectoral, axillary, periaortic, iliac	Axillary (3 cm)	HHV8-MCD Mixed type	2	2	3	1	2	Positive	<100/HPPF	<40%	Polyclonal	None	Pleural effusion, ascites, splenomegaly	First-line therapy: CVP Second-line therapy: IEV Third-line therapy: Valganciclovir Death by relapse disease
14	70/F	Axillary, periaortic	Axillary (5 cm)	HHV8-MCD Plasma cell type	1	1	2	3	3	Positive	<100/HPPF	<40%	Polyclonal	ESR >15 mm/h, Hb <11.5 g/dL, albumin level <3.5 g/dL, polyclonal hypergammaglobulinaemia >1.7 g/dL, renal failure	Ascites	Valganciclovir, death within 3 months from diagnosis
15	83/F	Both sides of the diaphragm	Axillary (1.7 cm)	HHV8-MCD Mixed type	1	2	2	3	2	Positive	<100/HPPF	<40%	Polyclonal	Hb <12.5 g/dL, renal failure, ESR >15 mm/h	Fatigue and hepatomegaly	Corticosteroids, death by cardiac disease
16	74/F	Both sides of the diaphragm	Axillary (2 cm)	HHV8-MCD Mixed type	2	2	2	1	3	Positive	<100/HPPF	<40%	Polyclonal	ESR >15 mm/h, albumin level <3.5 g/dL, Hb <12.5 g/dL	Fever and night sweats	Rituximab + valganciclovir, alive
17	82/F	Mediastinal, axillary, cervical, supraclavicular, inguinal	Cervical (2 cm)	HHV8-MCD Mixed type	2	2	2	1	3	Positive	<100/HPPF	<40%	Monoclonal	ESR >15 mm/h, CRP >10 mg/L, Hb <12.5 g/dL, albumin level <3.5 g/dL, polyclonal hypergammaglobulinaemia >1.7 g/dL, renal failure, thrombocytopenia	Fever	Corticosteroids, death within 1 month from diagnosis
18	50/F	Axillary and cervical	Axillary (2.5 cm)	POEMS-MCD Mixed type	2	1	0	1	3 (lambda-restricted)	Negative	<100/HPPF	<40%	n.v.	Platelet alterations, IgG lambda paraprotein	Polyneuropathy, sclerotic bone lesions, plasmacytoma	ASCT, alive
19	36/F	Mesenteric, inguinal, abdominal, pelvic	Axillary (4 cm)	POEMS-MCD Mixed type	3	3	2	0	2 (lambda-restricted)	Negative	n.v.	n.v.	n.v.	ESR >15 mm/h, CRP >10 mg/L, albumin level <3.5 g/dL, renal failure, IgG lambda paraprotein	Polyneuropathy, hepatomegaly, splenomegaly, pleural effusion, ascites, hypothyroidism, adrenal insufficiency	First-line therapy: ASCT Second-line therapy: CyBorD protocol Third-line therapy: Lenalidomide + dexamethasone Death by disease progression
20	42/M	Mediastinal, mesenteric, abdominal, inguinal	Inguinal (1.1 cm)	POEMS-MCD Plasma cell type	1	1	2	2	3 (lambda-restricted)	Negative	n.v.	n.v.	Monoclonal	IgG lambda paraprotein	Polyneuropathy, splenomegaly	Lost at follow-up
21	71/M	Axillary, cervical, inguinal, iliac	Inguinal (1 cm)	iMCD mixed type	3	2	3	0	3 (lambda-restricted)	Negative	<100/HPPF	<40%	Monoclonal	ESR >15 mm/h, CRP >10 mg/L, albumin level <3.5 g/dL, IgG lambda paraprotein	Hepatomegaly	Lost at follow-up
22	57/F	Mediastinal, axillary, cervical, supraclavicular	supraclavicular (1.7 cm)	iMCD mixed type	1	1	2	2	2	Negative	<100/HPPF	<40%	Polyclonal	ESR >15 mm/h, CRP >10 mg/L, Hb <11.5 g/dL, albumin level <3.5 g/dL, thrombocytopenia	None	Rituximab, alive

(Continues)

TABLE 3 (Continued)

Case ID	Age/sex	Involved lymph nodes	Biopsy site (size)	Diagnosis	Regressed GC[a]	FDC hyperplasia[a]	Vasculature[a]	Hyperplastic CG[a]	Plasmacytosis[a]	HHV8	IgG4 plasma cells	IgG4/IgG ratio	IGH clonality	Laboratory criteria	Clinical criteria	Treatment and follow-up
23	45/M	Abdominal mass, mesenteric, inguinal	Retroperitoneal (7 cm)	iMCD mixed type	3	1	2	0	3	Negative	>100/HPF	<40%	Polyclonal	ESR >15 mm/h, CRP >10 mg/L, Hb <12.5 g/dL, albumin level < 3.5 g/dL, polyclonal hypergammaglobulinaemia >1.7 g/dL and thrombocytosis	Weight loss and fatigue	Surgical excision of the abdominal mass, alive
24	81/M	Mediastinal, axillary, inguinal, abdominal, pelvic	Axillary (4.5 cm)	iMCD mixed type and ISFN	1	1	1	2	2	Negative	<100/HPPF	<40%	Monoclonal	ESR >15 mm/h, CRP >10 mg/L, Hb <12.5 g/dL, albumin level < 3.5 g/dL, renal failure, thrombocytosis	Fever, weight loss and fatigue	Siltuximab, death by infectious complications
25	58/M	Mediastinal mass and mediastinal lymph nodes	Mediastinal (4.5 cm)	iMCD mixed type	3	2	3	0	2	Negative	<100/HPPF	<40%	Polyclonal	ESR >15 mm/h, CRP >10 mg/L, Hb <12.5 g/dL, albumin level < 3.5 g/dL, polyclonal hypergammaglobulinaemia >1.7 g/dL	Fever, weight loss, fatigue and night sweats	Siltuximab, alive
26	73/M	Both sides of the diaphragm	Axillary (3.5 cm)	iMCD mixed type	3	2	2	0	2	Negative	<100/HPPF	<40%	Polyclonal	ESR >15 mm/h, CRP >10 mg/L, Hb <12.5 g/dL, IgG kappa paraprotein	Fever, fatigue and splenomegaly	Siltuximab, death by EBV-positive DLBCL
27	18/M	Mediastinal mass	Sovraclavear (3.5 cm)	iMCD mixed type	3	2	2	2	2	Negative	<100/HPPF	<40%	Polyclonal	ESR >15 mm/h, CRP >10 mg/L, Hb <12.5 g/dL	Fatigue, splenomegaly, pericardial effusion	Siltuximab, alive
28	25/F	Mesenteric and periaortic	Mesenteric (4.5 cm)	iMCD mixed type	2	2	2	2	2	Negative	<100/HPPF	<40%	Polyclonal	Splenomegaly and polyclonal hypergammaglobulinaemia >1.7 g/dL	Fatigue	Siltuximab in program, alive
29	63/F	Bilateral axillary	Axillary (3 cm)	iMCD mixed type	2	2	2	2	3	Negative	<100/HPPF	<40%	Polyclonal	ESR >15 mm/h, CRP >10 mg/L, Albumin level < 3.5 g/dL, Hb <12.5 g/dL	Fatigue	Siltuximab, alive

Abbreviations: ASCT, autologous stem cell transplantation; CVP, cyclophosphamide, vincristine sulphate and prednisone; CyBorD, cyclophosphamide, bortezomib and dexamethasone; DLBCL, diffuse large B-cell lymphoma; IEV, ifosfamide, epirubicin and etoposide; ISFN, in situ follicular B-cell neoplasm.

[a]A score from 0 to 3 was assigned as reported by Fajgenbaum et al.[6]

Clinicopathological features of POEMS-MCD

The three patients diagnosed with POEMS-MCD were two females and one male, with a median age of 43 years (age range 36–50). All patients were HIV– and at the last follow-up, one was alive, one died of multiple myeloma and one was lost. The axillary lymph nodes (diameter: 2.5, 4 and 1.1 cm) showed mixed-CD in two cases and P-CD in one case. HHV8 was negative in all the cases. There was no significant increase in IgG4 plasma cells in the evaluated case. The first patient was affected from solitary lambda-restricted plasmacytoma of the scapula associated with polyneuropathy, hypothyroidism, thrombocytosis, multiple lymphadenopathies, osteosclerotic lesions, an IgG lambda serum paraprotein, and polytypic plasma cells in the bone marrow biopsy. The second patient had polyneuropathy, hepatosplenomegaly, hypothyroidism under replacement therapy, adrenal insufficiency, oedema and dry skin, an IgA lambda serum paraprotein and bone marrow infiltration by lambda-restricted plasma cells. Both patients showed mixed-CD with lambda light chain-restricted plasma cells in the lymph nodes, but IGH rearrangement could not be assessed because of the low quality of the extracted DNA. The third patient was affected from a demyelinating polyneuropathy with an IgA lambda serum paraprotein, splenomegaly and bone marrow infiltration by lambda-restricted plasma cells. The excised lymph node showed a P-CD with lambda-restricted plasma cells and evidence of a minor monoclonal IGH rearrangement on a polyclonal background.

Clinicopathological features of iMCD

Nine iMCD cases fulfilled both the two major diagnostic CDCN criteria[6] and showed at least two minor clinical criteria, including a minimum of one laboratory criterion. Infectious, autoimmune and malignant diseases were excluded in all the cases. The patients were all adults (six males and three females, median age 54.5 years, range 18–81). Treatments were heterogeneous over the years: five patients received siltuximab, and one will start it within 1 week; one was administered rituximab, one was treated exclusively with surgical excision of the bulky mass and one was lost to follow-up. Two patients died from infectious complications or subsequent EBV-positive diffuse large B-cell lymphoma.

The involved lymph nodes were mediastinal, supraclavicular, axillary, cervical and mesenteric (mean diameter 3.7 cm, range 1–7). All the cases showed mixed-CD histology, and all were HHV8-negative. No significant increase in the IgG4 plasma cell count and/or in IgG4/IgG ratio was found in all the cases. Monoclonal IGH gene rearrangement in a polyclonal background was observed in two cases. The first patient (Case 21) was a mixed-MCD with lambda-restricted

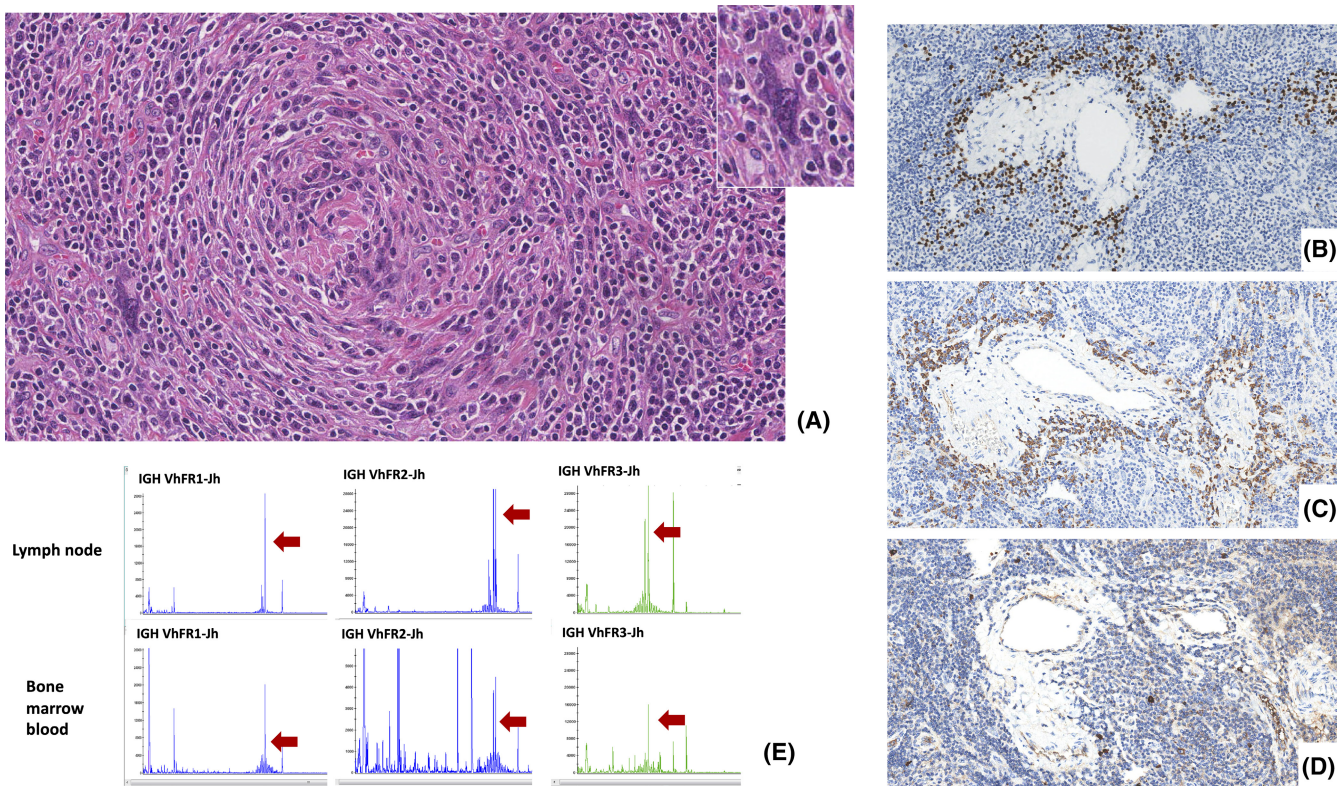

FIGURE 1 Histology of UCD with atrophic follicles (A, haematoxylin and eosin (H&E), original magnification (o.m. ×280), follicular dendritic cells dysplasia (insert, o.m. ×400) and hypervascular interfollicular areas. Perivascular plasma cells with k light chain-restricted expression (B, mum1; C, kappa; D, lambda; all o.m. ×200). Gene scan analysis for IGH gene rearrangement showed high peaks (red arrows) with the same molecular weight in both the lymph node and the bone marrow biopsies (E).

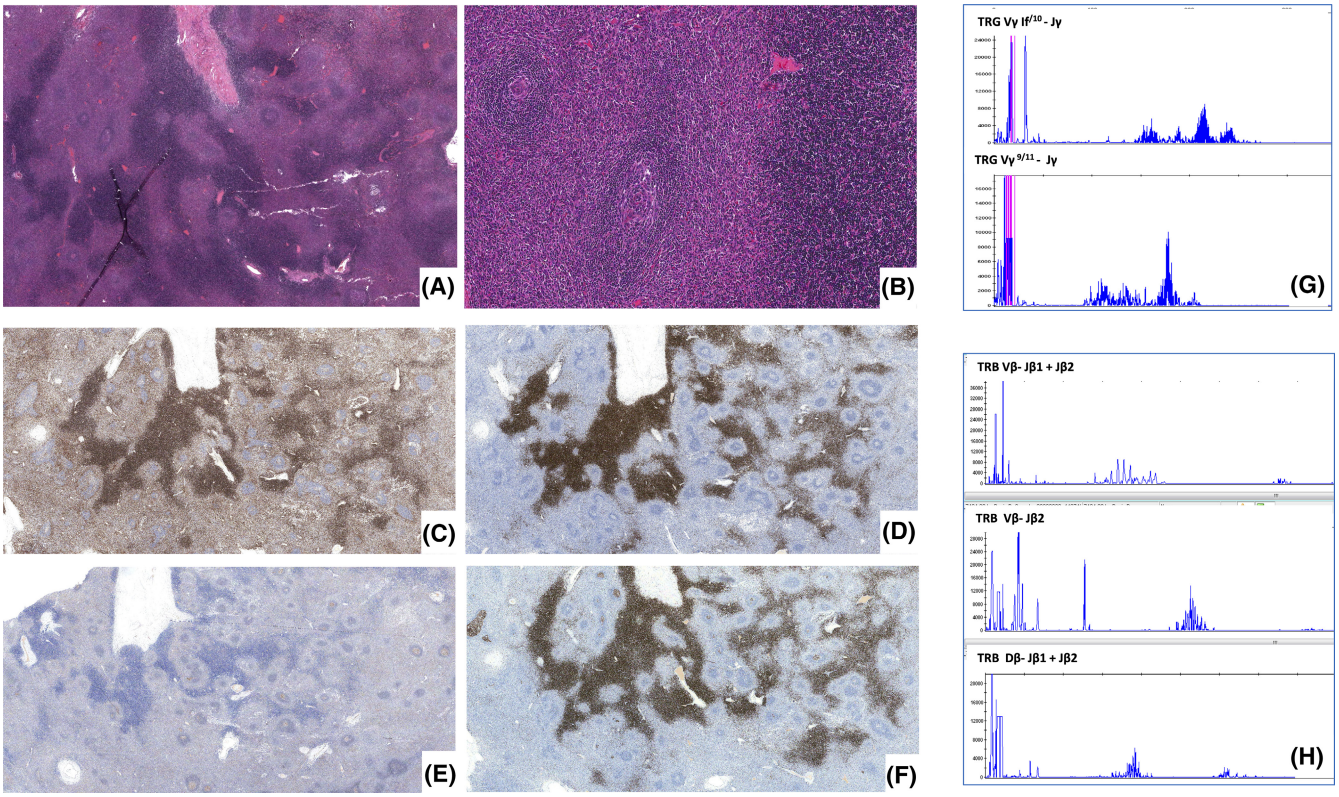

FIGURE 2 Histology of UCD Case 8 (A, ×13) showing HV-CD with interfollicular proliferation of immature T-cell lymphocytes (B, H&E, o.m. ×100) positive for CD3 (C, o.m. ×13) and TDT (D, o.m. ×13) and negative for LMO2 (E, o.m. ×13). The proliferation index was high (F, Ki-67, ×13). T-cell clonality assays demonstrated polyclonal rearrangements of both TRG (G) and TRB (H) genes.

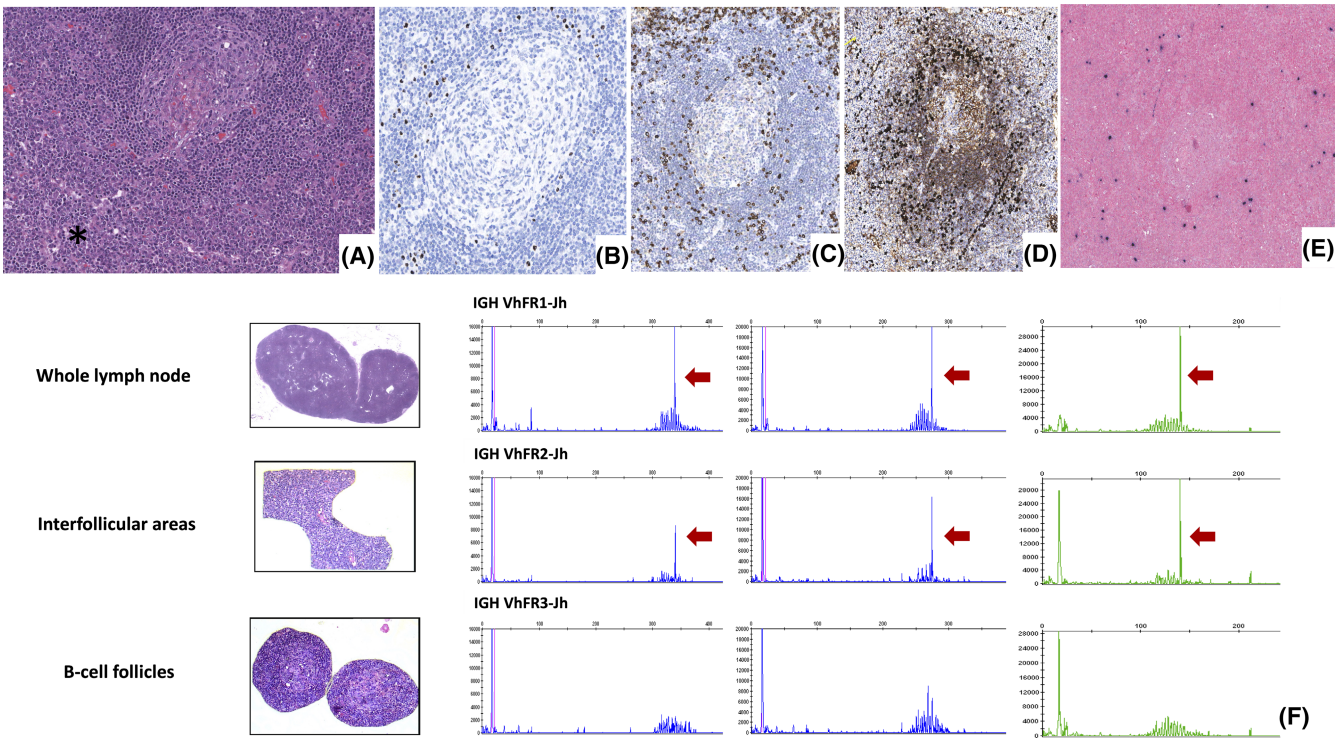

FIGURE 3 HHV8-MCD with lollipop follicles, numerous interfollicular plasma cells (asterisk) (A, haematoxylin and eosin, o.m. ×100), and HHV8-infected (B, LANA1, o.m. ×200) IgM+ (C, o.m × 130), Lambda+ (D, o.m. ×130) plasmablasts located within the follicular mantle zones. Some EBV-infected cells were present in the interfollicular areas (E, EBER, ×100). Clonality analysis (F) performed on the DNA extracted from the whole lymph node and from the microdissected interfollicular areas and B-cell follicles showed the presence of the same clonal peak (red arrows) in the whole lymph node and in the interfollicular areas but not in the follicles.

plasma cells and an IgG lambda paraprotein in serum in the absence of polyneuropathy and with a 5% of lambda-restricted plasma cells in the bone marrow biopsy compatible with a MGUS. The absence of polyneuropathy in this patient excluded POEMS diagnosis. The second patient (Case 24) showed a mixed-CD with some follicles partially populated by centrocytes with intense coexpression of CD10 and BLC2 consistent with a concomitant in situ follicular B-cell neoplasm (ISFN) (Figure 4). This patient benefitted from siltuximab administration with remission of symptoms and stable lymph nodes but died of infectious complications after 12 months from diagnosis.

Clinicopathological features of CD-like lymphadenopathies

In 19 cases, the diagnosis of CD was not confirmed after the review of clinical and laboratory data, although some histological features could suggest CD. Of these, one patient was diagnosed with ALPS, while three patients were found to have autoimmune diseases, such as RA (one case) and SLE (two cases). The final diagnosis of mixed connective tissue disease (MCTD) associated with CD-like lymphadenopathy was made in the other two patients due to the lack of laboratory findings supporting iMCD.

In one of the patients with MCTD, an increased number of tissue IgG4 plasma cells (75/HPF) with a high IgG4/IgG ratio (>40%) and increased IgG4 serum levels (440 mg/dL) but normal IgGA serum levels (172 mg/dL) were observed. However, clinical and radiological data excluded the diagnosis of IgG4-RD. This was instead confirmed in a patient with a history of pulmonary hyalinizing granuloma and focal pleural thickening in whom all required pathological and laboratory criteria were met (tissue IgG4 > 100; tissue IgG4/IgG >40%; serum IgG4 = 579.5 mg/dL; serum IgG4/IgG = 66.3). In addition, IgA plasma cells in the lymph node were rare (Figure 5), and serum values of IgA (183 mg/dL) and IgM (148 mg/dL) were normal, ruling out the alternative diagnosis of an iMCD with high serum levels of IgG4.[24–26]

The patient with ALPS was a 22-year-old male with cervical lymphadenopathy. The histology of the excised lymph node showed follicular hyperplasia with some regressive germinal centres with penetrating blood vessels and occasional twinning (Figure 6). A perifollicular granuloma associated with IgG4 plasma cells was also noted. The interfollicular area was expanded by polytypic plasma cells and double-negative T-cell lymphocytes (CD3+, CD4− and CD8−) with scattered proliferating immunoblasts. High IgG4 serum levels (428.5 mg/dL), 18% of double-negative T cells and mutation of the *TNFRSF6* were detected in the peripheral blood.

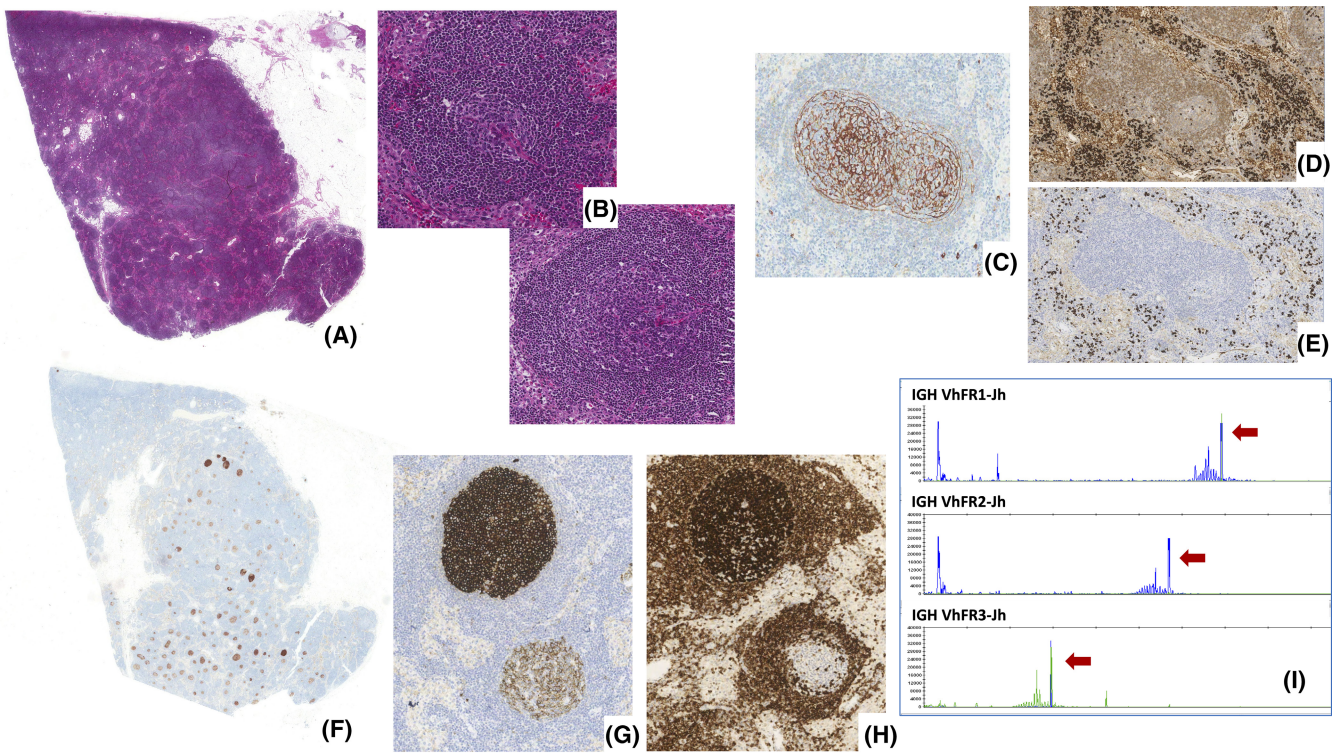

FIGURE 4 Histology of patient 24. A 4.5-cm lymph node (A; H&E, o.m. ×5) with open sinuses, hyperplastic and regressed follicles with some vessels radially penetrating the germinal centres (lollipop feature) (B, H&E, o.m. ×150), occasional twinning of germinal centres (C; CD21, o.m. ×100) and mild interfollicular polytypic plasmacytosis (D; Kappa, o.m. ×84; E; Lambda, o.m. ×84). Scattered hyperplastic germinal centres were populated by monomorphic centrocytes with intense coexpression of CD10 (F; o.m. ×5; G, o.m. ×100) and BLC2 (H, o.m. ×100). IGH gene clonality assay showed a mild prominent peak on a polyclonal background supporting the coexistence of an in situ follicular B-cell neoplasm (ISFN) within a MCD.

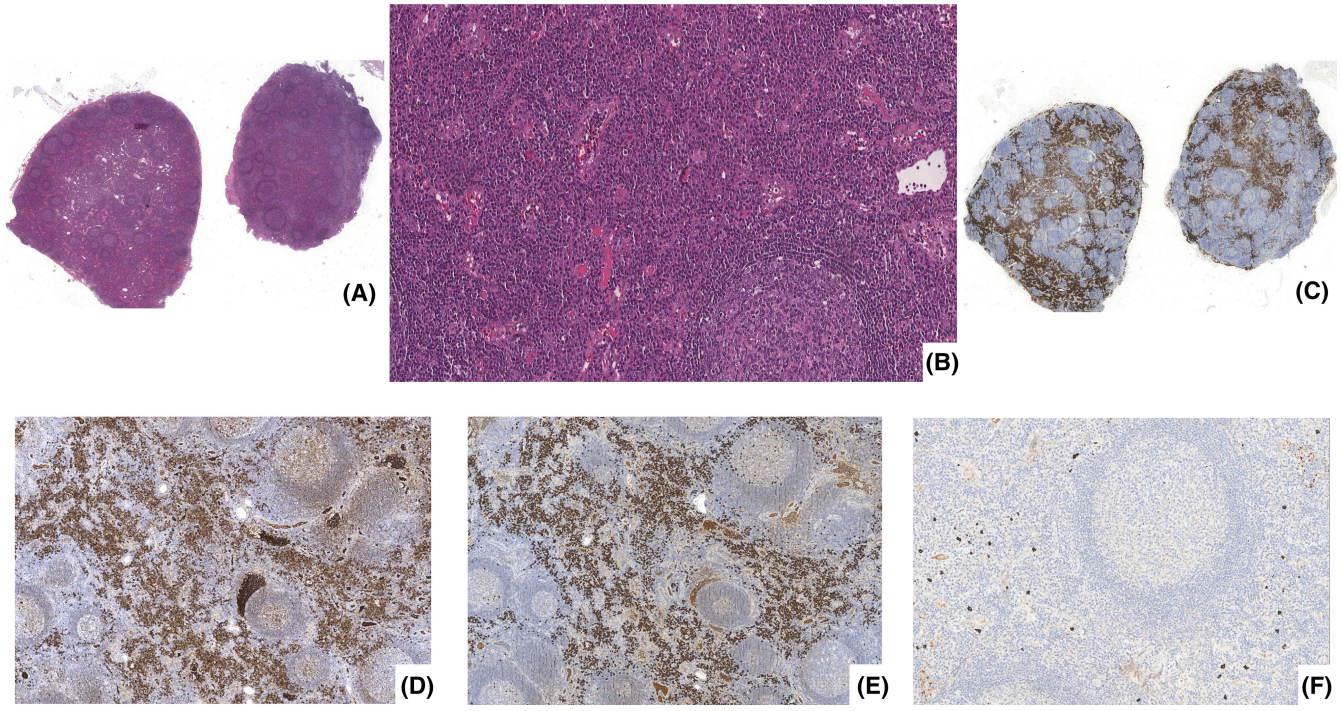

FIGURE 5 Histology of patient affected by IgG4-RD (A, H&E, o.m. ×7; B, H&E, o.m. ×130). Hyperplastic follicles were surrounded by numerous IgG4 plasma cells with IgG4/IgG ratio > 40% (C, CD138, o.m. ×7; D, IgG, o.m. ×30; E, IgG4, o.m. ×30). Only rare IgA-positive cells were observed (F, IgA, o.m. ×150).

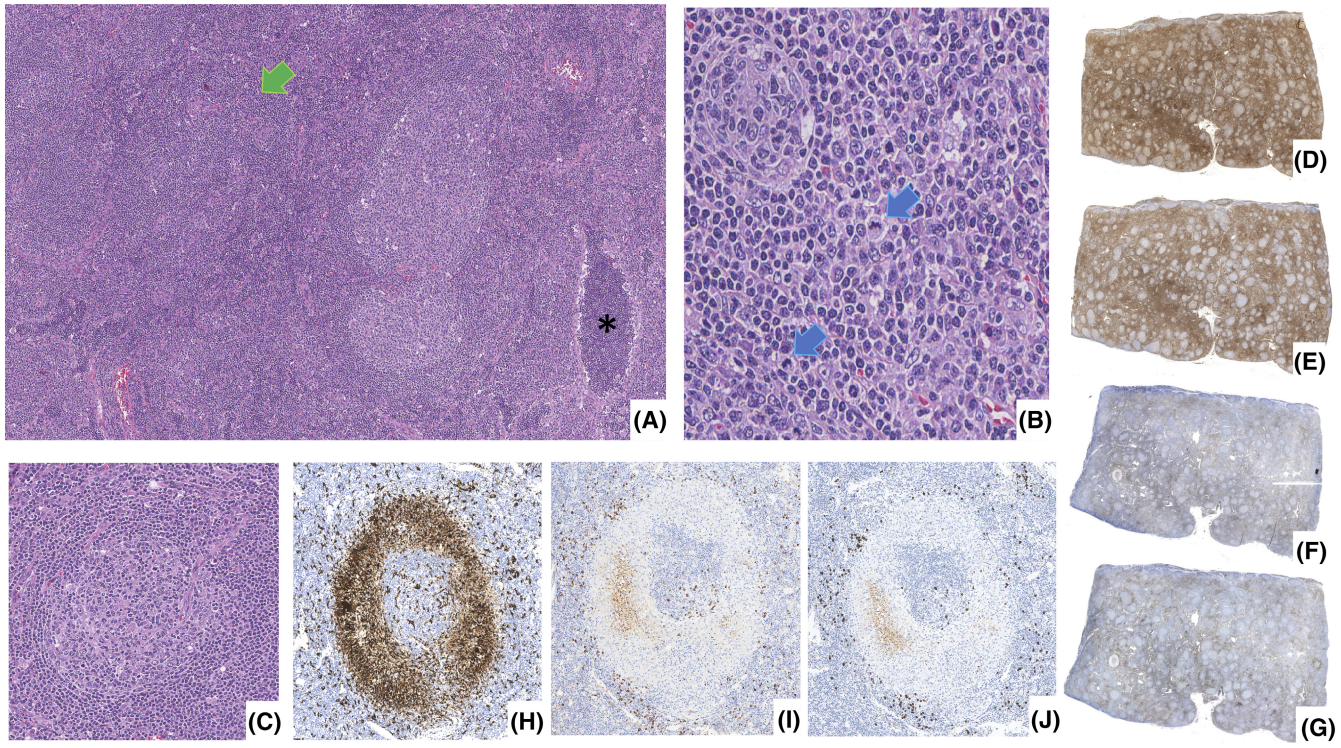

FIGURE 6 Histology of a patient with ALPS showing some follicles with atrophic germinal centres (green arrow), twinning (A, H&E, o.m. ×60), and lollipop appearance (C, H&E, o.m. ×200). Vessels were filled by small lymphocytes (A, asterisk), and the interfollicular areas (B, H&E, o.m. ×400) were expanded and populated by small lymphocytes and some proliferating immunoblasts (blue arrows), expressing CD3 (D, o.m. ×4), and CD5 (E, o.m. ×4), and only in part CD4 (F, o.m. ×4) and CD8 (G, o.m. ×4). Perifollicular granuloma composed of a ring of CD68+ macrophages (H, o.m. ×80) and some IgG+ (I, o.m. ×80) and IgG4+ (J, o.m. ×80) plasma cells.

Of the remaining 12 patients, 11 (one HIV-infected) were diagnosed with reactive lymphadenitis because the laboratory and/or histological criteria for MCD were not fully met.

The last case was the most complicated to diagnose. The patient had supra- and sub-diaphragmatic lymphadenopathy, bilateral pleural effusion, leuco and thrombocytopenia. The mediastinal biopsy was represented by two lymph node fragments, one showing CD-like features and the other one with an expanded interfollicular proliferation of B cell admixed with T lymphocytes infiltrating the perinodal adipose tissue (Figure 7). IGH clonality assay showed a prominent peak on a polyclonal background. In light of these findings, a diagnosis of NMZL associated with CD features was made, and treatment with rituximab was started.

DISCUSSION

The diagnosis of CD implies combining a compatible histopathological pattern with knowledge of the patient's complete clinical history. We pathologically and clinically reviewed 49 cases with CD-like histology, confirming the diagnosis of CD in 60% of the cases. Most of them were UCD or MCD associated with HHV8 infection or POEMS. This result highlights the importance of the HV histological features usually found in the UCD, the identification of the HHV8+ plasmablasts for HHV8-MCD and the association of a monotypic tissue plasmacytosis with the presence of a plasma cell clone and neurological symptoms for the diagnosis of POEMS-MCD. An exception to this rule was represented by Case 1, the HV-UCD with FDC dysplasia and a minor IgM kappa plasmacytosis in both the lymph node and the bone marrow. This case suggests that, similar to POEMS-MCD, a circulating B-cell clone could also localize in an otherwise typical UCD.

Integrating clinical, laboratory and imaging data was essential for a conclusive diagnosis in multicentric lymphadenopathies with histological aspects compatible with mixed-CD. Indeed, the diagnostic criteria for RA, LES and ALPS were met in four patients, while in two patients, a diagnosis of CD-like lymphadenopathy associated with MCTD was suggested because the required laboratory findings for CD were not present. High tissue IgG4 plasma cells and IgG4 serum levels were found in one of the patients with MCTD, but the diagnostic criteria for IgG4-RD were not satisfied. These cases represent the grey area of CD associated with autoimmune diseases, which may be simultaneously or subsequentially diagnosed, making treatment challenging.[27–30] This scenario is further complicated by the possibility that a lymphoproliferative disorder may show CD-like features.[31–34] One of our patients was diagnosed with NMZL, in which the CD-like features could either be induced by the clonal B-cell proliferation or represent the background where the clonal proliferation subsequentially developed.

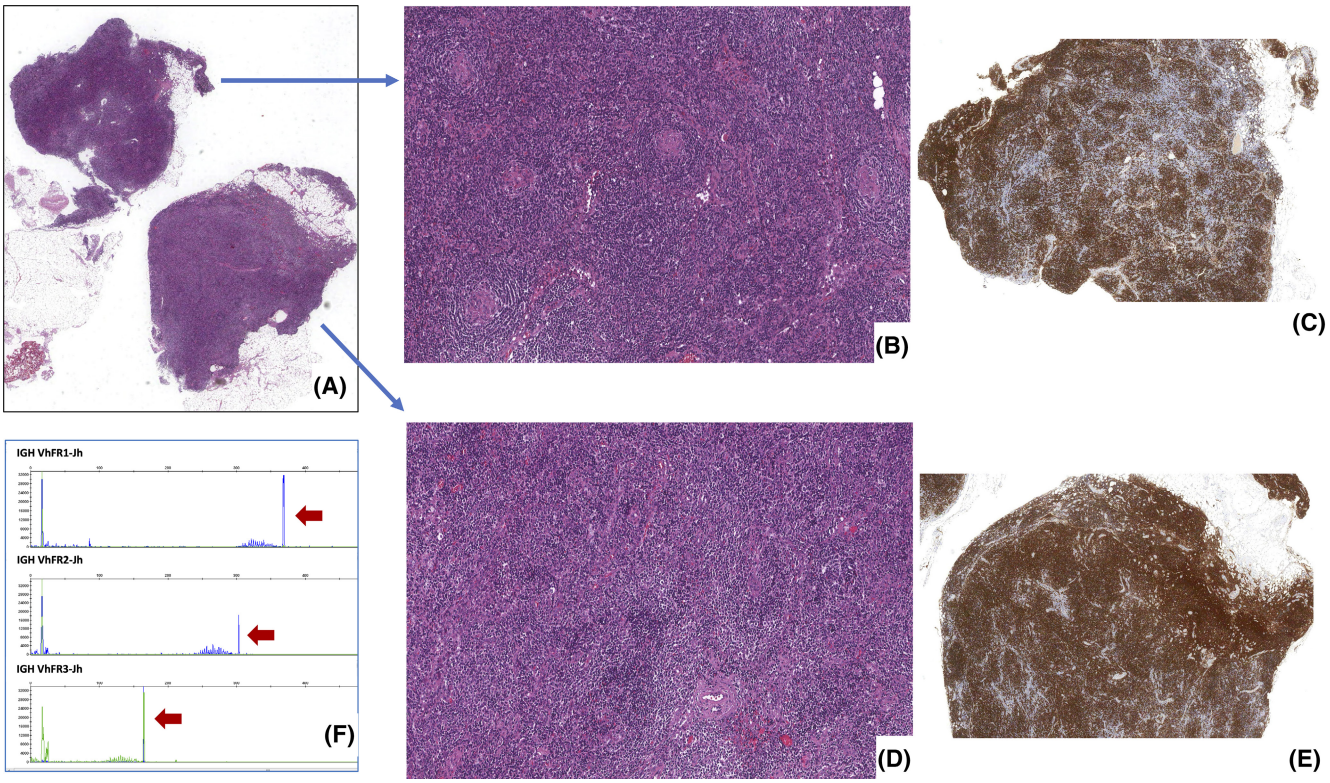

FIGURE 7 Nodal marginal zone lymphoma (A; H&E, o.m. ×8) showing focal CD-like areas (B, o.m. ×100) in which the B cells were mainly confined to the follicles (C, CD20, o.m. ×25) and other areas with loss of the normal lymph node architecture by a follicular and interfollicular B-cell expansion extending into the perinodal adipose tissue (D, H&E, o.m. ×100; E, CD20, o.m. ×25). IGH gene clonality analysis showed a high peak (red arrow) over a small polyclonal background (F).

As in other reports,[10,31,35–41] in our series the presence of a monoclonal IGH rearrangement was not a typical feature of CD and, when present, a possible explanation was given. In the literature, 13 CD have been found to have monoclonal rearranged IGH.[35–41] Of these, one was a plasma cell type UCD in which immunohistochemistry for kappa and lambda was not conclusive and no data on the presence of a serum M protein was reported,[35] four were POEMS-MCD,[37,41] three were iMCD and two of these had EBV DNA copies in the lymph nodes,[38] four had a concomitant haematological disease (two mantle cell lymphoma, one Hodgkin lymphoma and one multiple myeloma)[39] and one was an HIV+ patient with an incomplete IG rearrangement.[36] In our series, we found a monoclonal IGH rearrangement in 1/12 UCD (8.3%) and in 4/15 MCD (26.7%). The UCD had tissue monotypic plasma cells and an associated IgM MGUS. Of the MCD, two cases were associated with MGUS with one meeting the criteria for POEMS, whereas one was partially involved by ISFN. Tamber et al., by reviewing 11 cases of ISFN, described 2 cases in lymph nodes with Castleman-like disease and with IgG4-RD respectively, suggesting that ISFN may be a marker of B-cell dysfunction.[42] The fourth case was instead an HHV8-MCD in which the reactivation and clonal expansion of interfollicular EBV-infected B cells related to the CD-induced immune dysregulation was postulated. This hypothesis is in line with that suggested by Hanson et al., who found a minor IGH rearrangement in two patients with plasma cell variant of CD in whom EBV genome copies were detected in the examined lymph nodes.[38]

On the other hand, molecular analyses were fundamental to support the suspicion of NMZL with CD-like features in one of our cases and to exclude the diagnosis of lymphoblastic T-cell lymphoma in UCD with a concomitant indolent T-cell lymphoblastic proliferation in another one.

In conclusion, our study showed that, by applying the recently established consensus clinicopathological criteria for CD and combining them with clonality studies, we could refine the initial diagnosis of lymphadenitis with CD-like features, making a conclusive diagnosis of CD in 61% of the cases. This confirms the crucial role of the multidisciplinary approach to the diagnosis of reactive lymphadenitis with CD-like features. We therefore propose pathologist to make a diagnosis consistent with CD in patients with compatible clinical, radiological and laboratory data, whereas to suspect CD in lymphadenitis with convincing histopathological features but in whom a comprehensive workout to exclude IgG-RD, autoimmune disorders, ALPS and infectious diseases still have to be performed.

AUTHOR CONTRIBUTIONS

Arianna Di Napoli and Sabrina Pelliccia designed the study. Arianna Di Napoli, Evelina Rogges and Sabrina Pelliccia drafted the manuscript. Arianna Di Napoli, Evelina Rogges and Antonello Cardoni performed histological revision of the slides. Gianluca Lopez and Stefania Scarpino performed molecular analysis. Arianna Di Napoli, Stefano Fratoni, Daniele Remotti, Carla Giordano, Antonella Bianchi and Rita De Vito were responsible for histopathological diagnosis. Arianna Di Napoli was responsible for molecular diagnosis. Sabrina Pelliccia, Agostino Tafuri, Katia Girardi, Esmeralda Conte, Maria Paola Bianchi, Anna Laura Faccini, Katia Girardi, Ombretta Annibali, Gioia De Angelis, Flavia Del Porto and Francesca Di Gregorio were responsible for clinical diagnosis. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no associations or financial disclosures to report that could create a conflict of interest with the information presented in this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available within the article and from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and performed in accordance with the ethical requirements of biomedical research promulgated by the international and national governments. Ethical approval CE 7361/23.

PATIENT CONSENT STATEMENT

All patients have signed written informed consent.

ORCID

Arianna Di Napoli https://orcid.org/0000-0002-3159-5380

REFERENCES

1. Castleman B, Towne VW. Case records of the Massachusetts General Hospital; weekly clinicopathological exercises; founded by Richard C. Cabot. N Engl J Med. 1954;251(10):396–400.
2. Dispenzieri A. POEMS syndrome: 2017 update on diagnosis, risk stratification, and management. Am J Hematol. 2017;92(8):814–29.
3. Kawabata H, Takai K, Kojima M, Nakamura N, Aoki S, Nakamura S, et al. Castleman-Kojima disease (TAFRO syndrome): a novel systemic inflammatory disease characterized by a constellation of symptoms, namely, thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly: a status report and summary of Fukushima (6 June, 2012) and Nagoya meetings (22 September, 2012). J Clin Exp Hematop. 2013;53(1):57–61.
4. Lachant NA, Sun NC, Leong LA, Oseas RS, Prince HE. Multicentric angiofollicular lymph node hyperplasia (Castleman's disease) followed by Kaposi's sarcoma in two homosexual males with the acquired immunodeficiency syndrome (AIDS). Am J Clin Pathol. 1985;83(1):27–33.
5. Nicoli P, Familiari U, Bosa M, Allice T, Mete F, Morotti A, et al. HHV8-positive, HIV-negative multicentric Castleman's disease: early and sustained complete remission with rituximab therapy without reactivation of Kaposi sarcoma. Int J Hematol. 2009;90(3):392–6.
6. Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, et al. International, evidence-based consensus diagnostic criteria for

HHV-8-negative/idiopathic multicentric Castleman disease. Blood. 2017;129(12):1646–57.
7. van Rhee F, Voorhees P, Dispenzieri A, Fosså A, Srkalovic G, Ide M, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018;132(20):2115–24.
8. van Rhee F, Oksenhendler E, Srkalovic G, Voorhees P, Lim M, Dispenzieri A, et al. International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease. Blood Adv. 2020;4(23):6039–50.
9. Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood. 2020;135(16):1353–64.
10. Chang KC, Wang YC, Hung LY, Huang WT, Tsou JH, Jones DM, et al. Monoclonality and cytogenetic abnormalities in hyaline vascular Castleman disease. Mod Pathol. 2014;27(6):823–31.
11. Cokelaere K, Debiec-Rychter M, De Wolf-Peeters C, Hagemeijer A, Sciot R. Hyaline vascular Castleman's disease with HMGIC rearrangement in follicular dendritic cells: molecular evidence of mesenchymal tumorigenesis. Am J Surg Pathol. 2002;26(5):662–9.
12. Pauwels P, Dal Cin P, Vlasveld LT, Aleva RM, van Erp WF, Jones D. A chromosomal abnormality in hyaline vascular Castleman's disease: evidence for clonal proliferation of dysplastic stromal cells. Am J Surg Pathol. 2000;24(6):882–8.
13. Li Z, Lan X, Li C, Zhang Y, Wang Y, Xue W, et al. Recurrent PDGFRB mutations in unicentric Castleman disease. Leukemia. 2019;33(4):1035–8.
14. Fajgenbaum DC, Langan RA, Japp AS, Partridge HL, Pierson SK, Singh A, et al. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. J Clin Invest. 2019;129(10):4451–63.
15. Arenas DJ, Floess K, Kobrin D, Pai RL, Srkalovic MB, Tamakloe MA, et al. Increased mTOR activation in idiopathic multicentric Castleman disease. Blood. 2020;135(19):1673–84.
16. Pierson SK, Shenoy S, Oromendia AB, Gorzewski AM, Langan Pai RA, Nabel CS, et al. Discovery and validation of a novel subgroup and therapeutic target in idiopathic multicentric Castleman disease. Blood Adv. 2021;5(17):3445–56.
17. Gérard L, Bérezné A, Galicier L, Meignin V, Obadia M, De Castro N, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB trial. J Clin Oncol. 2007;25(22):3350–6.
18. van Rhee F, Fayad L, Voorhees P, Furman R, Lonial S, Borghaei H, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. J Clin Oncol. 2010;28(23):3701–8.
19. Krishnan J, Danon AD, Frizzera G. Reactive lymphadenopathies and atypical lymphoproliferative disorders. Am J Clin Pathol. 1993;99(4):385–96.
20. Frizzera G, Peterson BA, Bayrd ED, Goldman A. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: clinical findings and clinicopathologic correlations in 15 patients. J Clin Oncol. 1985;3(9):1202–16.
21. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181–92.
22. Di Napoli A, Rogges E, Noccioli N, Gazzola A, Lopez G, Persechino S, et al. Deep sequencing of immunoglobulin genes identifies a very low percentage of monoclonal B cells in primary cutaneous marginal zone lymphomas with CD30-positive Hodgkin/Reed-Sternberg-like cells. Diagnostics (Basel). 2022;12(2):290.
23. Rogges E, Pelliccia S, Lopez G, Barresi S, Tafuri A, Alaggio R, et al. Angioimmunoblastic T-cell lymphoma with exuberant CD30-positive follicular dendritic cell proliferation in a SARS-CoV-2 patient: the role of mutational analysis to exclude an associated follicular dendritic cell sarcoma. Int J Mol Sci. 2022;23(16):9349.
24. Manabe A, Igawa T, Takeuchi M, Gion Y, Yoshino T, Sato Y. Immunohistochemical analysis of IgA expression differentiates IgG4-related disease from plasma cell-type Castleman disease. Med Mol Morphol. 2017;50(1):34–41.
25. Satou A, Notohara K, Zen Y, Nakamura S, Yoshino T, Okazaki K, et al. Clinicopathological differential diagnosis of IgG4-related disease: a historical overview and a proposal of the criteria for excluding mimickers of IgG4-related disease. Pathol Int. 2020;70(7):391–402.
26. Nishikori A, Nishimura MF, Nishimura Y, Notohara K, Satou A, Moriyama M, et al. Investigation of IgG4-positive cells in idiopathic multicentric Castleman disease and validation of the 2020 exclusion criteria for IgG4-related disease. Pathol Int. 2022;72(1):43–52.
27. De Marchi G, De Vita S, Fabris M, Scott CA, Ferraccioli G. Systemic connective tissue disease complicated by Castleman's disease: report of a case and review of the literature. Haematologica. 2004;89(4):ECR03.
28. Chrispal A, Vasuki Z, Thomas EM, Boorugu HK. Mixed connective tissue disorder and Castleman's disease. J Assoc Physicians India. 2010;58:515–7.
29. Muskardin TW, Peterson BA, Molitor JA. Castleman disease and associated autoimmune disease. Curr Opin Rheumatol. 2012;24(1):76–83.
30. Nakazato Y, Tsuchida S, Takada-Owada A, Onozaki M, Noda S, Nozawa Y, et al. Castleman disease and mimickers: clinicopathological findings of atypical lymphoproliferative disorders associated with autoimmune disease. J Clin Exp Hematop. 2022;62(3):119–26.
31. Pina-Oviedo S, Miranda RN, Lin P, Manning JT, Medeiros LJ. Follicular lymphoma with hyaline-vascular Castleman-like features: analysis of 6 cases and review of the literature. Hum Pathol. 2017;68:136–46.
32. Siddiqi IN, Brynes RK, Wang E. B-cell lymphoma with hyaline vascular Castleman disease-like features: a clinicopathologic study. Am J Clin Pathol. 2011;135(6):901–14.
33. Igawa T, Omote R, Sato H, Taniguchi K, Miyatani K, Yoshino T, et al. A possible new morphological variant of mantle cell lymphoma with plasma-cell type Castleman disease-like features. Pathol Res Pract. 2017;213(11):1378–83.
34. Oksenhendler E, Boutboul D, Fajgenbaum D, Mirouse A, Fieschi C, Malphettes M, et al. The full spectrum of Castleman disease: 273 patients studied over 20 years. Br J Haematol. 2018;180(2):206–16.
35. Al-Maghrabi J, Kamel-Reid S, Bailey D. Immunoglobulin and T-cell receptor gene rearrangement in Castleman's disease: molecular genetic analysis. Histopathology. 2006;48(3):233–8.
36. Goyal G, Kendric K, Silberstein PT, Caponetti GC, Vivekanandan R. Multicentric Castleman disease with monoclonal incomplete IgH restriction: a rare coexistence. J Clin Exp Hematop. 2015;55(2):103–8.
37. Hall PA, Donaghy M, Cotter FE, Stansfeld AG, Levison DA. An immunohistological and genotypic study of the plasma cell form of Castleman's disease. Histopathology. 1989;14(4):333–46.
38. Hanson CA, Frizzera G, Patton DF, Peterson BA, McClain KL, Gajl-Peczalska KJ, et al. Clonal rearrangement for immunoglobulin and T-cell receptor genes in systemic Castleman's disease. Association with Epstein-Barr virus. Am J Pathol. 1988;131(1):84–91.
39. Soulier J, Grollet L, Oksenhendler E, Micléa JM, Cacoub P, Baruchel A, et al. Molecular analysis of clonality in Castleman's disease. Blood. 1995;86(3):1131–8.
40. Butzmann A, Kumar J, Sridhar K, Gollapudi S, Ohgami RS. A review of genetic abnormalities in unicentric and multicentric Castleman disease. Biology (Basel). 2021;10(4):251.
41. Gould SJ, Diss T, Isaacson PG. Multicentric Castleman's disease in association with a solitary plasmacytoma: a case report. Histopathology. 1990;17(2):135–40.
42. Tamber GS, Chévarie-Davis M, Warner M, Séguin C, Caron C, Michel RP. In-situ follicular neoplasia: a clinicopathological spectrum. Histopathology. 2021;79(6):1072–86.

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