

CASE SERIES

Real-practice management and treatment of idiopathic multicentric Castleman disease with siltuximab: a collection of clinical experiences

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Abstract

Castleman disease (CD) is a group of lymphoproliferative disorders that share common histopathological features yet have widely different aetiologies, clinical features and grades of severity as well as treatments and outcomes. Siltuximab is currently the only therapy approved by the FDA and EMA for idiopathic multicentric CD and is recommended as first-line therapy in treatment guidelines. Despite the extensive characterization of siltuximab treatment in clinical trials, available evidence from real-world practice is still scant. This collection of clinical experiences focuses on patients treated with siltuximab therapy, particularly regarding the idiopathic multicentric CD diagnostic work-up, and on treatment administration in patients with complex disease entering differential diagnosis with CD or concomitant

diseases. Thus, these data help further characterize and improve the use of siltuximab in real practice in terms of effectiveness and safety of long-term administration as well as consequences of treatment interruption.

Keywords: idiopathic multicentric Castleman disease, management, siltuximab, treatment.

Citation

Rossini B, Cecchi N, Clemente F, De Paolis MR, Hohaus S, Innaro V, Lucignano M, Massaiu R, Palumbo G, Rigolin GM, Rossi FG, Verga L, Guarini A. Real-practice management and treatment of idiopathic multicentric Castleman disease with siltuximab: a collection of clinical experiences. *Drugs Context*. 2024;13:2023-9-4. <https://doi.org/10.7573/dic.2023-9-4>

Introduction

Castleman disease (CD) is a group of lymphoproliferative disorders that share common histopathological features with widely different aetiologies, clinical features and grades of severity as well as treatments and outcomes.¹ The unicentric CD variant presents as lymphadenopathy at a single anatomic site, whereas multicentric CD (MCD) involves multiple regions of lymphadenopathy and encompasses a human herpesvirus-8 (HHV8)-associated MCD (often in patients immunocompromised with HIV)

and an idiopathic variant (iMCD).² Recently, the Castleman Disease Collaborative Network (CDCN) proposed a classification system maintaining the unicentric CD versus MCD nomenclature but further dividing MCD by aetiological driver (HHV8-associated MCD (HHV8-MCD), POEMS syndrome-associated MCD and iMCD) and classifying iMCD by phenotype (iMCD-TAFRO and iMCD-not otherwise specified).² Despite the pathogenesis not being fully elucidated, IL-6 and other cytokines have been evoked as common drivers for the cytokine storm that underlies the clinical manifestations of disease variants.³ One-third to one-half of MCD cases occur in patients

who are HHV8 and HIV negative and are referred to as HHV8-negative MCD or iMCD.^{1,2}

The epidemiology of iMCD is poorly understood because of the rarity of the disease and the difficulty of diagnosis, leading to it being underdiagnosed. A recent study in the USA estimated an annual incidence and prevalence of iMCD of 3.4 and 6.9 cases per million, respectively.⁴ Historically, patients with iMCD have a poor prognosis. Indeed, the 5-year overall survival rate varies considerably amongst cohorts, ranging from 35% to 77%.^{5,6}

The diagnosis of CD can be difficult, even with modern diagnostic tools. Particularly, the diagnosis of CD requires pathological examination of an affected lymph node performed from an excisional biopsy and observation of macroscopic architectural features.¹ The pathological features are then integrated with a syndromic clinical evaluation (minor criteria: laboratory criteria and clinical criteria) to confirm the iMCD diagnosis (Box 1).¹ Finally, exclusion of autoimmune diseases, infectious conditions and onco-haematological diseases is required.⁶ Furthermore, a differential diagnosis should be made between iMCD, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell neoplasm and skin changes), and TAFRO syndrome (poorer prognosis, with the clinical characteristics being thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly).⁷

Several treatment approaches have been used for the management of iMCD in the last decades, including corticosteroids, B cell-depleting agents, chemotherapies, immunomodulators and, more recently, IL-6-targeted monoclonal antibody therapies.^{4,8} Since 2012, the CDCN has established the current state of medical management of CD and made an immense effort to accelerate the search for patients with treatment-refractory CD.^{6,9}

To date, siltuximab, a monoclonal antibody targeting IL-6, is the only therapy for iMCD approved by the FDA and EMA; it is recommended as first-line therapy in treatment guidelines.^{8,9} In a randomized phase II study, 34% of 53 patients treated with siltuximab achieved the primary endpoint of durable tumour and symptomatic responses, compared with 0% of the best supportive care arm.⁹ In the long-term extension analysis of two trials including 60 patients with a stable or improved disease with siltuximab therapy, 100% of patients were alive at 6-year follow-up, 97% had disease control at their last on-study evaluation and 76% of patients completed the study after 6 years with disease control.¹⁰ Siltuximab was well tolerated across all clinical trials, with few serious adverse events or discontinuations and a long-term safety profile.^{10–12}

Despite the extensive characterization of siltuximab treatment in clinical trials,^{9–11} the available evidence from real-world practice is still scant.^{5,12,13} In order to further characterize and improve the use of siltuximab in real practice in terms of effectiveness and safety of long-term administration and on consequences of treatment interruption, this collection of clinical experiences focuses on patients on siltuximab therapy, particularly regarding the iMCD diagnostic work-up and treatment administration in patients with complex disease entering differential diagnosis with CD or with concomitant diseases.

Patients and methods

The authors retrospectively selected and reported on newly diagnosed iMCD clinical cases, highlighting the challenge of the diagnostic work-up and detailed consequences of long-term treatment with siltuximab as well as cases of patients with concomitant diseases and experiencing treatment interruption. Inclusion criteria were age ≥ 18 years and a diagnosis of iMCD based on the major and minor inclusion criteria and exclusion criteria (Box 1);⁶ indication of treatment with siltuximab was based on clinical practice and physician judgment. All patients were negative for HHV8 according to the criteria for the diagnosis of iMCD⁶ and to comply with the siltuximab Summary of Product Characteristics.¹⁴ Treatment with siltuximab was prescribed as monotherapy or in addition to other concomitant therapeutic regimens^{8,9} and was administered according to the doses and modalities defined in the Summary of Product Characteristics. Because of the retrospective description of this case series, treatment regimens and patient education were not standardized.

The study was conducted following the ethical principles of the revised version of the Declaration of Helsinki and notified to the Ethics Committee of IRCCS oncology institute 'Gabriella Serio' (Bari, Italy). Participants signed an informed consent form for publication of the details of the medical case and any accompanying images.

Clinical experiences

A total of ten clinical experiences are reported, three related to patients with complex disease and concomitant diseases, six related to the long-term administration of siltuximab and one case regarding the consequences of treatment interruption. A summary of demographic and clinical characteristics of patients is reported in Table 1.

Box 1. Criteria for idiopathic multicentric Castleman’s disease diagnosis.

Inclusion criteria
Major criteria (need both) - Histopathological lymph node - Lymphadenopathy in ≥2 lymph node stations
Minor criteria (need ≥2 out of 11 with at least one laboratory criterion) Laboratory - Elevated erythrocyte sedimentation rate or C-reactive protein - Anaemia - Thrombocytopenia/thrombocytosis - Renal dysfunction or proteinuria - Polyclonal hypergammaglobulinaemia - Hypoalbuminaemia Clinical - Constitutional symptoms - Large spleen and/or liver - Fluid accumulation - Eruptive cherry angioma or violaceous papules - Lymphocytic interstitial pneumonitis
Exclusion criteria
Infection-related disorders - HHV8 - Epstein-Barr virus lymphoproliferative disease - Inflammation and adenopathy by other infection
Autoimmune/inflammatory disease - Systemic lupus erythematosus - Rheumatoid arthritis - Adult-onset Still disease - Juvenile idiopathic arthritis - Autoimmune lymphoproliferative syndrome
Malignant lymphoproliferative disorder - Lymphoma - Multiple myeloma - Primary lymph node plasmacytoma - Follicular dendritic cell sarcoma - POEMS syndrome

iMCD diagnosis and siltuximab treatment in patients with complex disease and concomitant diseases

Case 1

In September 2021, a 64-year-old woman presented with a 2-week history of persistent diarrhoea, abdominal pain, fever, night sweats and laterocervical lymphadenopathy. The patient also reported episodes of spontaneous eyelid angioedema and abdomen skin rash. Four years earlier, the patient had been diagnosed with Sjogren’s syndrome but required no therapy. Whole-body computed tomography (CT) scan showed an enlarged liver (22 cm), thickened gallbladder walls, lymph nodes at the hepatic hilum (the largest measured 7 mm on the short axis), and normal-sized spleen and pancreas. Lumbar

aortic lymph nodes, endometrial thickening (7 mm), consolidation striae at the pulmonary bases, bilateral pleural and pericardial effusion (maximum 7 mm), bilateral laterocervical lymph nodes (up to 23×10 mm), and lymph nodes in the axillary and mediastinal regions were also observed. Laboratory examinations showed haemoglobin (Hb) levels of 12.7 g/dL, white blood cell (WBC) count of 10,500/mm³ (9120 neutrophils/mm³) and platelet count (PLT) of 268,000/mm³. The patient exhibited altered renal function (creatinine 1.65 mg/dL; estimated glomerular filtration rate, 32 mL/min), elevated inflammation parameters (C-reactive protein (CRP): 120.7 mg/L; normal range ≤0.8 mg/dL), reduced albumin levels (25 g/L; normal range: 34–54 g/L), increased α₁-globulin (11.9%) and α₂-globulin (19.8%) with normal γ-globulin (16.3%), and proteinuria (0.82 g/L). A whole-body positron

Table 1. Summary of demographic and clinical characteristics of patients.						
	Sex	Age (years)	IMCD type	Criteria for IMCD diagnosis ^a	Start of siltuximab therapy (11 mg/kg every 21 days)	Response to treatment
Case 1	W	64	IMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: altered renal function, elevated inflammation parameters, proteinuria	November 2021 - Transient increase in blood pressure following the first infusion, managed on an outpatient basis with no lasting effects - The patient has completed 21 cycles of treatment, without relevant side-effects	A complete morphological response was confirmed on the total body CT scan (March 2023)
Case 2	M	61	IMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: increased indices of inflammation, altered blood count, hypoalbuminaemia, polyclonal hypergammaglobulinaemia, oedema	December 2021 - Normalization of inflammation indices within the third infusion - Blood counts were normal after 6 months of treatment	Significant clinical improvement, with resumption of mobility with a marked reduction of joint pain
Case 3	W	56	IMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: worsening of renal function with the onset of proteinuria	May 2022 Before the fifth administration, the patient's clinical condition worsened with several episodes of acute abdomen and cerebral ischaemia requiring hospital admissions. The remission state of the IMCD condition after siltuximab administration led to the temporary discontinuation of siltuximab and the initiation of a specific autoimmune disorder treatment	Improved clinical condition related to cryoglobulinaemic vasculitis and is still undergoing rehabilitation to recover from ischaemic outcomes; the intention is to resume IMCD treatment with siltuximab as soon as the clinical conditions are fully stabilized
Case 4	M	60	IMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: increased erythrocyte sedimentation rate, increased indices of inflammation, polyclonal hypergammaglobulinaemia	July 2021 - Good clinical tolerance and rapid normalization of inflammation indices and hypergammaglobulinaemia - The patient has completed 27 cycles of treatment, without relevant side-effects	CT scan in January 2023 documented dimensional reduction of all lymph nodes, of all infracentimetric or pericentimetric dimensions, and further reduction of the right renal mass
Case 5	W	59	IMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: altered renal function, proteinuria	February 2021 The patient completed 43 cycles of treatment, without relevant side-effects	At the last visit (July 2023), the patient was asymptomatic and adherent to therapy

(Continued)

Table 1. (Continued)

	Sex	Age (years)	iMCD type	Criteria for iMCD diagnosis ^a	Start of siltuximab therapy (11 mg/kg every 21 days)	Treatment course	Response to treatment
Case 6	M	18	iMCD – mixed histological variant	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: systemic symptoms	January 2022	• An instrumental examination for disease re-evaluation is carried out every 6 months unless otherwise needed or clinical complications arise • The patient completed 20 cycles of treatment, without relevant side-effects	Significant improvement in QoL, with a total disappearance of clinical symptoms
Case 7	M	54	iMCD – hyaline-vascular type	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: increased indices of inflammation, altered blood count, hypoalbuminaemia, proteinuria	March 2019	• After the fifth administration, the patient presented a diffuse skin rash associated with pruritus. The therapy was temporarily suspended and resumed regularly after 5 months • The patient completed 61 cycles of treatment without relevant side-effects	Significant improvement in QoL, with a total disappearance of clinical symptoms
Case 8	F	49	iMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: increased indices of inflammation, hypoalbuminaemia, hypogammaglobulinaemia, proteinuria	January 2022	• The patient completed 18 cycles of treatment without relevant side-effects	Clear reduction in the spleen size and lymphadenopathy. No evidence of PLA4R antibodies, and proteinuria almost disappeared
Case 9	M	65	iMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: systemic symptoms	May 2021	• The patient completed 31 cycles of treatment without relevant side-effects	At the last follow-up (March 2023), the patient was in complete remission and had an excellent QoL
Case 10	M	18	iMCD with plasma cell-type histology	Major: histopathological lymph node, lymphadenopathy in ≥2 lymph node stations Minor: systemic symptoms	June 2021	• The patient completed 17 cycles of treatment without relevant side-effects	Marked improvement in QoL and a complete remission

^aAll patients were HHV8-negative at LANA1 test.
iMCD, idiopathic multicentric Castleman’s disease; QoL, quality of life.

After 2 weeks of prednisone therapy, the patient demonstrated significant clinical improvement, particularly a reduction in anasarca and normalization of Hb, creatinine, and albumin levels and a decrease in 24-h proteinuria (0.416 g/L). Subsequently, in November 2021, the patient started siltuximab therapy at 11 mg/kg every 21 days. Fol-

Case 2

In April 2021, a 61-year-old male patient was referred from the rheumatology department after a CT examination showed chest and abdomen adenopathy (2–4 cm maximum diameter). The patient had been diagnosed in 2017 with psoriatic/rheumatoid arthritis based on a family history of rheumatoid arthritis, and was unresponsive to various therapies (steroids and immunosuppressants, all discontinued since mid-2021). Reported symptoms were night sweats, marked asthenia, intense arthralgia with functional limitations and fever. CRP was 120 mg/L, and erythrocyte sedimentation rate (ESR) was 120/148/97 mm/h.

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The PET/CT scan performed the following month showed multiple supradiaphragmatic and subdiaphragmatic lymph node uptakes (SUV_{max} between 5.3 and 5.1 in the axillary and inguinal area, respectively) associated with intense tracer hyperfixation in the nasopharyngeal region (SUV_{max} 6.8). Widespread osteomedullary uptake was also reported in the proximal femoral tract and at the scapulohumeral and sternoclavicular joints. Physical examination confirmed the presence of lymphadenomegaly with a maximum diameter of about 2 cm at the axillary and inguinal bilateral level, which was mobile and soft in consistency.

A lymph node biopsy was performed, reporting a picture of lymphadenopathy with CD-like aspects; however, the diagnosis of iMCD was initially excluded because of the autoimmune disease in the patient history. Nevertheless, rheumatological consultation clarified that the diagnosis of psoriatic/rheumatoid arthritis in 2017 was performed by exclusion considering the patient's clinical features (arthralgia) and family history (father with psoriasis) without further clinical or instrumental support. Therefore, a comprehensive evaluation established a diagnosis of iMCD supported by the presence of increased indices of inflammation, altered blood count, hypoalbuminaemia, polyclonal hypergammaglobulinaemia, oedema, and absence of HHV8-positive elements after LANA1 test and neoplastic diseases, considering the reported rheumatological diagnosis implausible. The patient was started on siltuximab therapy (11 mg/kg) in December 2021, which is ongoing and repeated every 21 days.

Since the start of treatment, there has been significant clinical improvement, with the resumption of mobility with a marked reduction of joint pain, resolution of sloping oedema with an almost total ad integrum restitution of quality of life (QoL). These responses were accompanied by normalization of inflammation indices within the third infusion (ESR 35/73/35 mm/h after the second cycle, CRP <4 mg/L). After 6 months of treatment, blood counts were normal. CT scan and PET/CT scan showed persistence of supradiaphragmatic adenopathies, with dimensions between 1.5 and 2 cm, but a significant reduction in the size of abdominopelvic adenopathies (<2 cm diameter max versus 3.5 onset), with reduction of SUV in all lymph node stations. Reduced lymph node extension in the abdominopelvic site was reported. Bilateral tonsillar hyperfixation persisted. The patient is currently awaiting an annual CT scan re-evaluation.

Case 3

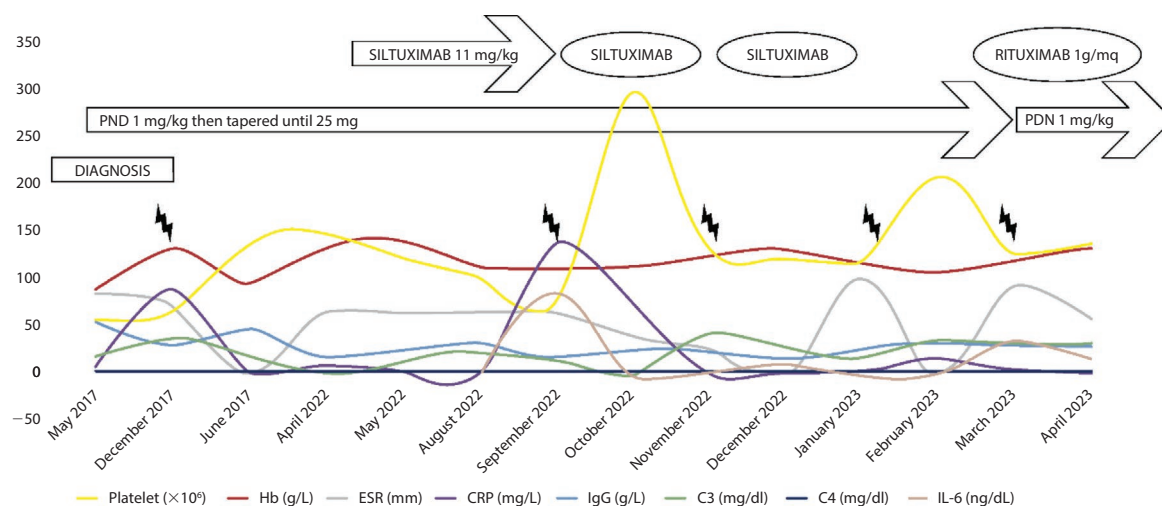
A 56-year-old female patient presented with asthenia, generalized pruritus and hyperpyrexia. Viral serological screening was negative. Upon diagnostic completion, the patient underwent an MRI abdomen and liver biop-

sy whose histological examination was conclusive for primary biliary cirrhosis, stage III. At the same time, a CT scan of the chest and abdomen showed the presence of abdominal, mediastinal and axillary adenopathies, the largest at the intercavaortic level (39×17 mm). An irregular parenchymal thickening process was visible in the left lower pulmonary lobe; PET images confirmed the involvement of lymph node, splenic and pulmonary sites. The histological examination of the lymph node showed preserved architecture, with lymphoid follicles with hyperplastic germinal centres (CD20⁺, CD10⁺, BCL6⁺, BCL2⁻, Ki67 elevated) with the normal distribution of CD21⁺CD23⁺ follicular dendritic cells, and some involutonal 'hyaline-vascular' aspects. The paracortical interfollicular region was markedly expanded, with prominent sinuses, and consisted mainly of large aggregates of plasma cells without significant cytological atypia, polyclonal for light chains, with a minor population of small lymphocytes with T phenotype; scattered eosinophilic granulocytes were associated. LANA1 test for HHV8 was negative. The patient was diagnosed with HHV8-negative iMCD with plasma cell-type histology. Concurrently, the patient reported progressive worsening of renal function with the onset of proteinuria (0.6 g/L). Renal biopsy showed the presence of interstitial T cell infiltration associated with few polyclonal plasma cells. The IgG/IgG4 ratio was 4:1. Histological examination was inconclusive for CD localization.

In June 2017, treatment with prednisone, 1 mg/kg per day, was set to manage iMCD, with progressive improvement in renal and hepatic function, normalization of plasma γ -globulins, and indices of systemic inflammation (Figure 2). However, during follow-up, the patient developed an infectious complication with septic shock, acute renal failure, encephalitis, paroxysmal atrial fibrillation and disseminated intravascular coagulation. Consequently, steroid therapy was reduced to a low-medium dose (25 mg daily). The patient maintained a good response and regression of symptoms for about 4 years.

In April 2022, the patient presented with night sweats and sporadic episodes of hyperpyrexia. Laboratory tests showed Hb 14.4 g/dL, PLT 124×10⁶, CRP 0.06 mg/dL, ESR 64 mm, IgG 22.60 g/L, IgA 3.9 g/L and IgM 13.3 g/L; PET/CT imaging confirmed stable lymphadenopathies, with intense FDG uptake in several lymph nodes. Given the severity of the clinical presentation and the patient's recurrence of symptoms, therapy with siltuximab, previously unavailable in Italy, was undertaken.

The first infusion of siltuximab (11 mg/kg every 21 days) was given in May 2022. However, in August 2022, before the fifth administration of siltuximab, the patient's clinical condition worsened with several episodes of acute

Figure 2. Blood parameters and patient's therapy history.

Hb, haemoglobin; PDN, prednisone; ⚡, hospital admissions.

abdomen and cerebral ischaemia requiring hospital admissions and invasive procedures (emergency laparotomies, multiple biopsy investigations, spinal sampling and very long motor rehabilitation paths) with a long convalescence. The case was then evaluated by a multi-disciplinary team (haematologists, immunologists, gastroenterologists and neurologists), and a diagnosis of type III cryoglobulinaemic vasculitis was made (with the presence of polyclonal IgM and IgG). However, the onset of vasculitis was not correlated with the administration of siltuximab due to the temporal gap between the administration of siltuximab and the onset of vasculitis (3 weeks later). The remission state of iMCD after siltuximab administration led to the temporary discontinuation of siltuximab and the initiation of a specific treatment for cryoglobulinaemic vasculitis, resulting in concomitant effectiveness for iMCD treatment. In detail, in April 2023, high-dose prednisone therapy (1 mg/kg) was started, with subsequent tapering and initiation of rituximab (1 g per two administrations every 15 days, as per rheumatological schedule), under close clinical-laboratory monitoring (Figure 2). Currently, the patient has an improved clinical condition related to cryoglobulinaemic vasculitis and is still undergoing rehabilitation to recover from ischaemic outcomes; the present intention is to resume iMCD treatment with siltuximab as soon as the clinical condition is fully stabilized.

Effectiveness and safety of siltuximab long-term administration in clinical practice

Case 4

In March 2021, a 60-year-old male patient was admitted to the medical oncology department on suspicion of

metastatic renal tumour. A renal mass biopsy was performed, and a histological examination was supportive of CD. The bronchial biopsy showed infiltration of lymphoid elements consisting of CD3⁺CD20⁻ T cells, mostly coexisting with polyclonal plasma cell infiltration with no light chain clonal expression on immunohistochemical examination; furthermore, negative determinations of TTF1, p40, HHV8 (LANA1 test), BCL2, BCL6 and low cytoproliferative activity of Ki67/MIB1 were demonstrated. The patient had a PET/CT scan with evidence of supra-diaphragmatic and subdiaphragmatic uptake referable to multiple lymph node swelling (the subcarinal site was the highest uptake site with SUV_{max} 15.6) and hypermetabolic nodular formations in the lungs as well as in the known formation of the right kidney (SUV_{max} 6.6). Steroid therapy was started. Biochemical tests showed normal blood count, increased ESR of 47 mm/h, and polyclonal hypergammaglobulinaemia of 30%. Liver, kidney and coagulation function tests were normal. A new total body CT scan was performed in June 2021. Initial reduction of pulmonary nodulations and supradiaphragmatic and subdiaphragmatic lymph nodes was observed as well as a right kidney mass infiltrating the hilum with overall dimensions of 75×51 mm versus 84×65. Surgical excision of the new right axillary lymph node was performed, and its histological examination confirmed the suspicion of HHV8-negative iMCD with plasma cell-type histology. Following a multidisciplinary evaluation, renal neoplasia was excluded as well as other neoplasms and the metastatic nature of the lymph nodes and pulmonary nodules. As confirmation of the CD diagnosis, a lung biopsy showed the presence of a lymphocytic infiltrate in this site (oriented for lymphocytic interstitial pneumonitis). Siltuximab therapy at a dosage of 11 mg/kg every 21 days was started in July 2021, with good clinical tolerance

and rapid normalization of inflammation indices and hypergammaglobulinaemia. A slight and temporary increase in transaminases was recorded. In December 2021, the re-evaluation documented good general clinical conditions, and the CT scan showed a dimensional reduction of pulmonary nodular formations and a slight reduction of renal mass and unchanged lymph nodes. In May 2022, the patient was still asymptomatic, with only mild arthralgias, with antinuclear antibody positivity 1:1280 speckled on biochemical investigations (the remaining autoimmunity tests were negative); the total body PET/CT scan evidenced a remarkable reduction in tracer accumulation at all sites. A CT scan in January 2023 (after 27 cycles of therapy) documented dimensional reduction of all lymph nodes, of all infracentimetric or pericentimetric dimensions, and further reduction of the right renal mass currently measuring 33 mm in diameter (*versus* 84 mm at diagnosis); small pulmonary parenchymal nodules also unchanged.

Case 5

In July 2020, a 59-year-old female patient presented with high-grade fever, weight loss, sweating, weakness and left supraclavicular swelling. The patient had been diagnosed with diabetes mellitus in 2015 and underwent surgery for megacolon in 2017. In March 2020, whilst admitted to the infectious disease ward, an ultrasound examination showed left supraclavicular lymphadenopathy and splenomegaly. After the medical examination, an excisional biopsy of the left supraclavicular lymph node was performed, and the haematology-dedicated pathologist identified hyaline-vascular type CD. Under the microscope, the follicles had two or more small germinal centres with hyaline deposits, and the mantle consisted of concentric layers of lymphocytes with an onion skin appearance. The interfollicular region had a proliferation of hyalin vessels. In immunohistochemical staining, germinal centres contained CD21⁺ and CD35⁺ follicular dendritic cells; the interfollicular regions contained CD3⁺ T lymphocytes and plasmacytic dendritic cells. The bone marrow biopsy showed normocellular marrow.

On blood tests, Hb was 8.3 g/dL, CRP was 60 mg/dL, ESR was 40 mm/h, albumin was 2 g/dL and estimated glomerular filtration rate was 96 mL/min. PET/CT scan revealed lymphadenopathy (3.5 cm, SUV 4.8) in the left supraclavicular and mesentery region (2.5 cm, SUV 3.8), pericardial effusion and splenomegaly (13 cm). Histopathology was negative at the LANA1 test for HHV8. After the diagnosis of iMCD in February 2021, the patient started siltuximab therapy (11 mg/kg every 21 days) and shortly after became asymptomatic; his QoL improved, and Hb increased to 12.5 g/dL, CRP decreased to 0.5 mg/dL. No evidence of superficial lymphadenopathy and splenomegaly was reported at the medical examination. In November 2021, serum protein electrophoresis revealed the

onset of monoclonal gammopathy IgG lambda (1.7 g/L), stable over time. No evidence of increased lymph node metabolism was reported at the PET/CT scan in November 2022. At the last visit (July 2023), after 43 cycles of therapy, the patient was asymptomatic and adherent to therapy. No infections or other adverse events occurred during therapy.

Case 6

An 18-year-old male patient presented with marked asthenia, pruritus in the lower limbs, profuse sweating, lymph nodes with altered architecture on ultrasound examination in the laterocervical, supraclavicular and axillary sites, and leukocytosis on blood count (Hb: 14 g/dL, WBCs: 44,960/mm³, neutrophil: 41,910/mm³, lymphocytes: 3,400/mm³, PLT: 323,000/mm³). A total body CT scan showed solid tissue in the right antero-inferior mediastinum measuring 13x10x16 cm, a 13-mm pericardial effusion, some lymphadenopathies in the right hilar as well as prevascular, paratracheal, lumbar aortic, inter aortocaval and paracaval lymphadenopathies. In November 2021, the patient underwent a biopsy of the right supraclavicular lymph node and started treatment with methylprednisolone (0.25 mg/kg/day) on the same date. On histological examination, the lymph nodes were characterized by lymphatic follicles of variable size and sclerosis, with predominantly atrophic germinal centres (CD10⁺, BCL6⁺, BCL2⁻), with an area of central sclerosis, sometimes vascularized. Reinforcement of the reticulum texture (CD21⁺, CD23⁺) was also observed. The mantle area (CD79a⁺, BCL2⁺) was slightly expanded with an onion-bulb appearance. A slight expansion of the paracortical region (CD3⁺, CD5⁺) was associated with a polytypical plasma cell proliferation (CD138⁺, kappa⁺ chains, lambda⁺ chains), consisting of closely cohesive plasma cells organized in cords. The sample was negative for cyclin D1 and HHV8 (LANA1 test). The picture described was consistent with CD of mixed histological variant. PET/CT scan confirmed the presence of a disease with high metabolic activity in the supradiaphragmatic lymph node. The patient started siltuximab therapy at 11 mg/kg/dose in January 2022. The therapy was administered regularly, every 21 days, without side-effects. The CT scan after the third dose showed a reduction in the size of the right anterior-inferior mediastinal tissue (11x9x12 cm), further reduced after the 6th (10x9x11 cm) and 12th (7.8x7.6x10 cm) doses. Pneumomediastinal effusion was occasionally found, requiring no surgical intervention but close monitoring in the hospital setting. Upon resolution of the pulmonary picture, the patient resumed siltuximab therapy without any complications or adverse events. Since diagnosis, the patient has reached the 20th infusion of siltuximab and is being followed by a multidisciplinary team involving various specialists including a haematologist, cardiologist, pulmonologist, radiologist and infectious disease specialist. An instrumental ex-

amination for disease re-evaluation is carried out every 6 months unless otherwise needed or clinical complications arise, with controlled and infrequent access to hospital. There has been significant improvement in QoL, with a total disappearance of clinical symptoms.

Case 7

In June 2018, a 54-year-old male patient presented with systemic symptoms, including fever associated with shaking chills, headache, vomiting and arthromyalgia. Instrumental examinations, specifically CT scan and ultrasound, showed pleural effusion and hepatosplenomegaly (liver 21 cm, spleen 13.7 cm). General examinations reported CPR 26.3 mg/dL, ESR 22 mm/h, Hb 10.2 g/dL, PLT 55,000/ μ L, albumin 3 g/dL, proteinuria (0.13 g/24 h) and γ -globulin 20.2%. PET/CT scan showed diffuse supradiaphragmatic and subdiaphragmatic uptake at the lymph node level and other sites, such as the spleen and right mammary parenchyma. The patient was initially managed in the infectious disease department and was then transferred to rheumatology, immunology and haematology care. Corticosteroid therapy was started. In December 2018, a left iliac lymph node was examined, leading to the diagnosis of CD with a histological appearance of hyaline-vascular type. HHV8 was negative (LANA1 test), non-TAFRO. In March 2019, the patient started siltuximab therapy (11 mg/kg every 21 days) with progressive tapering of the steroid. After the fifth administration, the patient presented a diffuse skin rash associated with pruritus. On suspicion of a drug reaction, later confirmed by the cutaneous biopsy, the therapy was temporarily suspended to conduct investigations; it was resumed regularly after 5 months. To date (July 2023), the patient has undergone 61 administrations. After 4 years, his QoL has certainly improved with the absence of symptoms.

Case 8

In 2017, a 49-year-old female patient presented with declivous, periorbital oedema and important asthenia. She showed significant proteinuria (5000 mg/24 hours). A renal biopsy demonstrated idiopathic membranous nephropathy. On blood tests, the patient had a good Hb level (14.6 g/dL); WBCs were 4880/mm³ with normal leucocyte formula, normal PLT (196,000/ μ L), creatinine within the normal range but hypoalbuminaemia (2.7 g/dL), CRP 2 mg/dL, and ferritinaemia 145 ng/mL. A total body CT scan showed splenomegaly (15 cm in longitudinal diameter) and multiple mesenteric adenopathies with reactive features (about 1 cm in diameter). A total body PET/CT scan showed no frankly active metabolic uptake. The patient was treated with rituximab (375 mg/m², weekly for 4 weeks) for glomerulonephritis. The patient achieved a reduction in declivous oedema, a partial reduction in proteinuria (1 g/24 hours) and a reduction in spleen size (12.5 versus 15 cm). Fever, night sweats and abdominal pain ap-

peared in 2021, and declivous oedema and a fine skin rash recurred. Blood tests showed neutrophilic leukocytosis (WBCs 16,000/ μ L), Hb within limits, PLT 100,000/ μ L, significant elevation of inflammation markers (CRP 25 mg/dL, procalcitonin 5 mg/dL), frank hypoalbuminaemia and hypogammaglobulinaemia, proteinuria (2460 mg/24 h) and frank increase in anti-PLA2R Ab titre. Mild renal impairment was also present (creatinemia: 1.5 mg/dL). All blood and urine cultures as well as serology investigations were negative. A total body CT scan showed the presence of pleuro-pericardial and peritoneal effusions, mediastinal-axillary lymphadenopathy (short axis max 1.2 mm), cecum wall thickening and splenomegaly (h 18 cm). PET/CT scan showed mild laterocervical, supraclavicular and retroclavicular, axillary, ileo-mediastinal, lumbar aortic, interaortocaval and para-aortic lymph node FDG uptake with a low SUV index. No improvement was observed despite antibiotic, antifungal and antiviral therapy. Lymphadenectomy was performed, showing lymphatic follicles with marked regression of the germinal centre, exhibiting aspects of hyaline-vascular transformation; the meshwork of dendritic follicular cells (CD23⁺) was preserved. The germinal centres were occupied by PAX5⁺CD20⁺CD10⁺BCL2⁻ cells and were negative for cyclin D1, with a marked increase in subcapsular and interfollicular plasma cells without evidence of clonal restriction for immunoglobulin light chains. HHV8 (LANA1 test) and CD30 were negative (Figure 3). The features were consistent with a Castleman-like lymphoproliferative disease. The patient had an ECOG >2, extravascular fluid accumulation and an Hb level less than 8 g/dL (without transfusion). Therefore, the patient met the criteria for severe CD. After lymphadenectomy, the patient was started on a high dose of 6-methyl-prednisolone at the dosage of 1 mg/kg for 5 days, followed by 1 mg/kg/die and siltuximab (11 mg/kg) using the once-weekly infusion schedule for 4 weeks, as outlined in the treatment guidelines.⁹ The patient's general condition and biochemical tests were evaluated daily.

After starting this combination therapy, the patient's general condition gradually improved. The fever rapidly disappeared, and there was an improvement in the PLT, a reduction in inflammation markers, an increase in Hb level and a recovery of albumin values. Siltuximab infusions were then continued at 11 mg/kg intravenously every 3 weeks and tapering of steroid therapy was started. To date, about 1.5 years after the start of therapy, the patient is still under treatment with siltuximab infusions every 3 weeks. The patient's general condition is good. About a year after the start of therapy, a CT scan was performed, showing a clear reduction in the spleen size and a reduction in lymphadenopathy. As of today, there is no evidence of PLA4R antibodies and proteinuria has almost disappeared.

Case 9

In July 2019, a 65-year-old male patient presented with asthenia and dyspnoea, hyperoxia and diffuse bone pain. CT examination showed numerous lymph nodes at the laterocervical and supraclavicular level; numerous lymph nodes were increased in volume at the left sub-pectoral site, with the largest axial lymph node measuring about 21×18 mm. Numerous lymph nodes were also found in the ileo-mediastinal site and in the aorto-pulmonary window. The mediastinal adipose tissue was thickened with numerous lymph node enlargements, the largest being 22×9 mm. Solid nodules of about 6×5 mm were found in the upper lingula segment and apico-dorsal segment of the left upper lobe. Lymph node packets with maximum axial dimensions of 21×10 mm were found in the hepatic hilum and portal seat with concomitant hepatomegaly. Total body PET examination showed tenuous fixation of the numerous lymph node stations described. A biopsy of the axillary lymph node was performed in August 2019. Histological examination showed preserved architecture with lymphatic follicles with involuted germinal centres and aspects of hyalinosis, increased follicular dendritic cells, and expansion of the mantle area. The follicles were CD20⁺ with regular BCL6⁺BCL2⁻ and elevated Ki67 germination centres. The lymphadenopathy had a Castleman-type architectural pattern. The patient was treated with six cycles of rituximab, cyclophosphamide, vincristine and prednisone (ended December 2019) with complete remission.

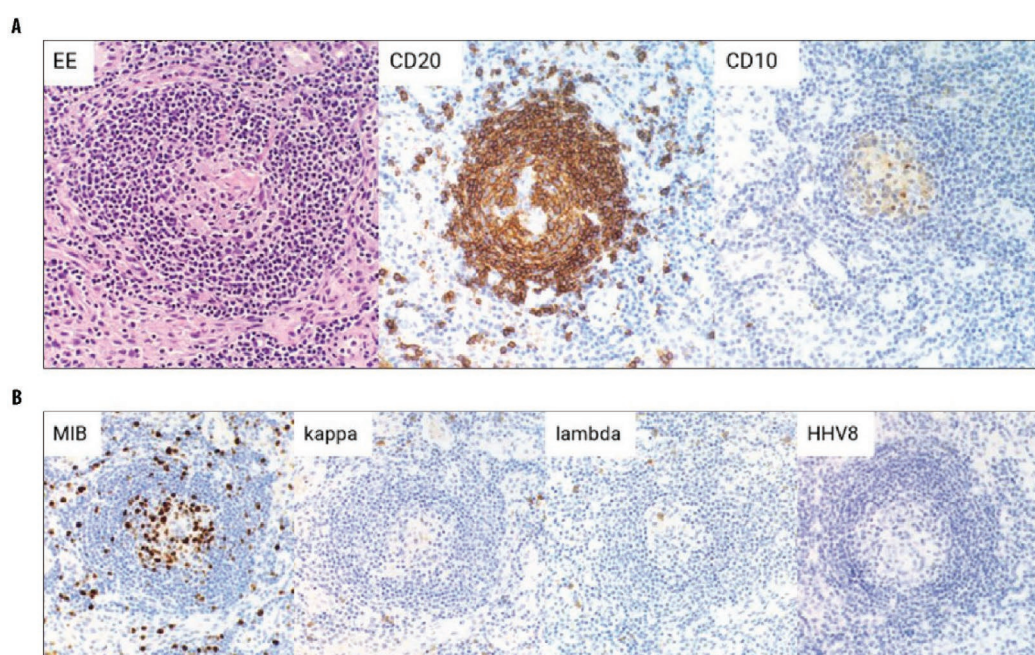
In May 2021, the patient recurred with abdominal pain and hyperpyrexia. A new biopsy on the axillary lymph node showed an overall preserved architecture with lymphatic follicles, concentric hyperplasia of the mantle, and involution of germinal centres with depleted sclerotic appearance and hyalinosis of the central follicular arteriole. The interfollicular areas were rich in vessels and polyclonal plasma cells. A subpopulation of IgA⁺ plasma cells was present. A regular distribution of immunoreactivity for CD3 and CD20 was reported, positive in the paracortical and cortical area, respectively, with hyperplasia of the CD21⁺ follicular dendritic cell networks; the sample was negative for HHV8 (LANA1 test) and Epstein–Barr virus. CD was diagnosed, and siltuximab therapy was started (11 mg/kg), with successive administration every 21 days. At the last follow-up (March 2023), after 31 administrations of siltuximab, the patient was in complete remission and had an excellent QoL.

Consequences of treatment interruption

Case 10

A 23-year-old male patient presented with adenopathy in the left axillary region associated with fever and night sweats. Axillary lymph node biopsy showed a morphological and immunophenotypic picture consistent with hyaline-vascular CD (HHV8 at LANA1 test and Epstein–Barr virus were negative). The patient was prescribed periodical use of non-steroidal anti-inflammatory drugs. In 2014, a reappearance of axillary adenopathy occurred

Figure 3. Lymphatic follicles with marked regression of germinal centres showing aspects of hyaline-vascular transformation; meshwork of dendritic follicular cells (CD23⁺) was preserved. The germinal centres were occupied by PAX5⁺CD20⁺CD10⁺BCL2⁻ cells. A marked increase in subcapsular and interfollicular plasma cells without evidence of clonal restriction for immunoglobulin light chains.



following a previous surgical exeresis. PET/CT scan showed retropectoral and axillary (SUV 2.1) and latero-cervical (SUV 2) uptakes. From September to December 2014, the patient was on cortisone therapy with no benefit. In December 2014, a biopsy of the axillary lymph node was repeated with confirmation of the diagnosis of hyaline-vascular iMCD disease, and treatment with non-steroidal anti-inflammatory drugs was resumed. In January 2021, the patient presented with full-body purple skin lesions, painful on palpation, intermittent, and associated with fever and night sweats. The symptoms persisted until June 2021. Laboratory tests, proteinuria and inflammation indices were normal. PET/CT scan showed diffuse lymph node uptake (SUV 2–3). As the major and minor criteria for the diagnosis of iMCD were met, in June 2021, the patient started therapy with siltuximab, 11 mg/kg every 21 days. In January 2022, disease assessment reported the absence of proteinuria and uptake areas; diffuse skin lesions had resolved. In April 2022, the patient decided, against medical advice, to suspend treatment. Skin lesions reappeared all over the body, and the patient decided to resume siltuximab therapy (11 mg/kg every 21 days). Skin lesions resolved after the first administration. To date, the patient has undertaken 17 infusions, which, unlike previous therapeutic approaches, resulted in marked improvement in QoL and complete remission.

Conclusion

iMCD is a rare lymph node disorder that can be under-diagnosed or misdiagnosed.¹ The delay in receiving a correct diagnosis represents a major barrier for patients in accessing effective therapy. In clinical practice, iMCD may be confused with other diseases with similar histopathology and symptoms, for example, autoimmune disorders (e.g. lupus), lymphoma, IgG4-related reactive lymphadenopathy with viral aetiology, sarcoidosis, amongst others.¹⁵ The CDCN diagnostic criteria state that disorders that may give rise to Castleman-like histopathology require specific exclusion (Box 1).⁶ However, iMCD can also occur in patients with a prior history of autoimmune disease, provided that this pathology is not in an active phase responsible for the clinical picture. For instance, the presence of autoimmune disease in a patient's medical history is not a negative predictor of the effectiveness of CD treatment.

Siltuximab is a monoclonal antibody that targets and neutralizes IL-6, a cytokine that plays a key role in developing iMCD. Currently, siltuximab is the only FDA/EMA-approved treatment for iMCD and for all patients with iMCD who are negative for HHV8 and HIV.^{8,9} As detailed in

the CDCN treatment guidelines, where available, siltuximab is the recommended treatment choice.⁸

Despite this recommendation, literature data report that siltuximab administration is underexploited in clinical practice.⁴ Indeed, amongst patients with iMCD in the USA, 39% received corticosteroid monotherapy, 33% received no iMCD-targeted treatment and less than 10% received IL-6-targeted therapy.⁴ In addition, few real-world studies on the use of siltuximab are available.^{5,13,14}

To provide further insight into the real-practice use of siltuximab, this clinical experience collection describes the approach to the iMCD diagnosis and siltuximab treatment in patients with complex disease entering differential diagnosis with CD or a concomitant disease, evaluating the effectiveness and safety of long-term administration and the consequences of treatment interruption.

The reported cases highlight the importance of a prompt diagnosis of iMCD as effective therapy is available. Moreover, given the complexity of iMCD, a multidisciplinary team approach involving haematologists, oncologists, rheumatologists, pathologists and other specialists is strongly suggested by these clinical experiences.

iMCD is a chronic disease that requires the continuous administration of siltuximab to maintain remission.^{16,17} Therefore, understanding the long-term safety and activity of siltuximab is fundamental.¹⁸ Consistent with the longest analysis of siltuximab treatment in patients with iMCD, the reported experiences support the effectiveness and safety of long-term administration of siltuximab, leading to long-term disease control in the absence of adverse events in the great majority of patients.¹¹ Furthermore, the effectiveness of siltuximab therapy in responding patients has increased over time, with the benefit of reducing lymph nodes or large masses. In these cases, responding treatment effectiveness is observed relatively quickly and significantly improves QoL related to near-normal living. Finally, further supporting the need for continuous administration of siltuximab, treatment discontinuation was associated with symptom relapse in the reported clinical experience.

Taken together, the reported experiences further support the indication of siltuximab in the first-line treatment of iMCD and represent proof-of-concept that its long-term administration improves patients' QoL and survival.

Availability of data

All data generated or analysed in this case series are included in this article and/or its figures. Further inquiries can be directed to the corresponding author.

Contributions: All authors contributed to the definition and contextualization of paper contents, critically edited the manuscript, and approved its final version for submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: <https://www.drugsincontext.com/wp-content/uploads/2024/02/dic.2023-9-4-COI.pdf>

Acknowledgements: Editorial and graphical assistance was provided by Simonetta Papa, PhD, Massimiliano Pianta, Valentina Attanasio and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by Recordati Rare Diseases.

Funding declaration: This study was conducted with an unconditioned educational grant from Recordati Rare Diseases.

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Article URL: <https://www.drugsincontext.com/real-practice-management-and-treatment-of-idiopathic-multicentric-castleman-disease-with-siltuximab-a-collection-of-clinical-experiences>

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Provenance: Submitted; externally peer reviewed.

Submitted: 26 September 2023; **Accepted:** 24 January 2024; **Published:** 12 March 2024.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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