Case Report

Idiopathic multicentric Castleman disease and connective tissue disorder successfully treated by siltuximab: a pediatric case report

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Background: Castleman disease (CD) is a rare lymphoproliferative disease. Idiopathic multicentric CD (iMCD), representing a distinct entity in CD, is partly attributed to autoimmune abnormalities and the hyperplastic process in iMCD involving the immune system. Consequently, iMCD presents a range of overlapping manifestations with connective tissue disorder (CTD), resulting in an inability to tell whether they coexist or imitate each other. Reports of CD combined with CTD are rare, more cases are needed to be summarized and analyzed to improve the efficiency of diagnosis and accelerate the development of novel treatments.

Case Description: A male pediatric patient was diagnosed with CTD in October 2019 and had been receiving regular treatment with tocilizumab and glucocorticoid or methotrexate since April 2020. He was further diagnosed with iMCD of the hyaline vascular subtype according to biopsy-proven histopathological features and imaging-proven multiple involvement in August 2021. He received 4 doses of rituximab and then a combination of thalidomide and dexamethasone for about 1 year. His clinical symptoms were well controlled throughout the disease for a long period, but inflammatory markers were repeatedly elevated, which eventually turned normal after switching to siltuximab from July 2023, although a significant elevation of interleukin-6 occurred.

Conclusions: We reported a pediatric case diagnosed as CTD and iMCD, whose inflammation finally be well controlled by siltuximab. Hopefully, our work will add insight into such rare situations and it is undoubtedly that the pathophysiological mechanism of CD and CTD coexistence and prediction models of treatment response remains to be explored to facilitate the clinical management and optimal treatment.

Keywords: Castleman disease (CD); connective tissue disorder (CTD); pediatric; case report; siltuximab

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Introduction

Castleman disease (CD), or giant lymph node (LN) hyperplasia, is a rare lymphoproliferative disorder of undetermined etiology, first reported in 1954 and named in 1956 by Benjamin Castleman (1). Unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) are two distinguished phenotypes with different extents of involvement and clinical course (2). MCD is characterized by generalized lymphadenopathy, systemic inflammatory symptoms, and even multiple organ/system dysfunction (3). Human herpes virus (HHV)-8-negative MCD, also known as idiopathic MCD (iMCD), accounts for at least one-third of all reported cases of MCD (4). The underlying pathogenesis may consist of autoimmunity/autoinflammation, paraneoplastic, and virus infection other than HHV-8 (3). Connective tissue disorders (CTDs) are a group of heterogeneous autoimmune diseases labeled by the presence of autoantibodies and certain clinical features, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome (SS) and polymyositis. Autoimmune abnormalities contribute to CD partly and on the other side, the hyperplastic process of CD involves the immune system. CD and CTD can be diagnosed simultaneously or they can mimic each other at the clinical and histopathological levels (2). Lack of profound knowledge of both respective and common characteristics of the two entities hinders the early diagnosis and optimal treatment.

Here we report a case of a male pediatric patient diagnosed successively with CTD and iMCD to gain a deeper insight into the coexistence of CD and CTD. We present this article in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-605/rc).

Highlight box

Key findings

- A male pediatric case diagnosed with connective tissue disorder (CTD) and idiopathic Castleman disease (CD), presented with a stable state but elevated inflammatory markers that was finally well controlled by siltuximab was reported herein.

What is known and what is new?

- We reported a rare pediatric case of a patient with idiopathic CD and CTD.
- The situation that has a stable clinical state but recurrent elevated inflammatory markers can be controlled by siltuximab.

What is the implication, and what should change now?

- Identifying potential predictive biomarkers of therapy response is essential for the timely treatment of patients like our case.
- The pathophysiological mechanism of CD and CTD coexistence remains to be explored.

Case presentation

History of CTD

A male patient born in February 2006 was diagnosed with polymyositis in another hospital (October 2019), on account of fever, myalgia and weakness in the upper limbs, positive myositis-specific antibodies [anti-MDA5 immunoglobulin G (IgG), IgG++, anti-Ku IgG+, anti-PM-Scl75 IgG++, anti-Mi-2β IgG+], high leukocytes count, and elbow joint effusion and abnormal muscle signals detected by magnetic resonance imaging (MRI) of the upper limbs. Regular treatment with methylprednisolone and mycophenolate mofetil was administered from then on. Muscle strength improvement, the disappearance of fever, and negative anti-MDA5 antibodies after treatment initiation all pointed to effectiveness. However, the suspicion lay in the persistent elevation of inflammatory markers [C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)] during follow-up and the appearance of low back pain.

With this in mind, the patient came to Children's Hospital of Fudan University in April 2020. Chest computed tomography (CT) showed multiple lymphadenopathies of the left axilla and mediastinum and the technetium bone scan showed foci of abnormal radiotracer concentration in T11, L2, and bilateral distal femurs. Integrating past medical history as well as newly detected positive antinuclear antibody (speckled pattern, 1:100), the diagnosis was modified to CTD (systemic juvenile idiopathic arthritis? Polymyositis?). The treatment regimen switched to a combination of prednisolone, naproxen, and periodic tocilizumab (320 mg, every 2 or 3 weeks). Prednisolone was gradually withdrawn (September 5, 2020) and methotrexate was added to the regimen (September 20, 2020).

About one year after the initiation of tocilizumab treatment, our patient visited us again complaining of bilateral calf myalgia for 2 weeks and consistently elevated inflammatory markers (June 2021). MRI of the lower limbs revealed multiple symmetrical lesions in the tibia, femur, and bone marrow cavity, but no significant tumor or inflammatory cells were shown on the tibial biopsy. The result of the technetium bone scan was improved, with only

abnormal foci in the left knee. The diagnosis was further amended to undifferentiated CTD and suspected chronic recurrent multifocal osteomyelitis (CRMO), without modification in the basic treatment plan (tocilizumab and methotrexate).

Diagnosis of iMCD

The patient was readmitted to our hospital on July 3, 2021, with a 5-day fever that could not be controlled by anti-infective therapy. Laboratory tests (*Table 1*) revealed mild anemia [hemoglobin (Hb) 107 g/L], elevated systematic inflammatory markers (leukocytes count 10.39×10^9/L; CRP 245.87 mg/L; serum amyloid A >550 mg/L; ESR 120 mm/h), decreased albumin (34.21 g/L), normal interleukin (IL)-6 (11.3 pg/mL) and high IL-8 (60.1 pg/mL). The coagulation function was dysregulated given the prolonged procalcitonin time (16.1 s), elevated D-dimer (0.97 mg/L), and fibrinogen (7.32 g/L). Antinuclear antibody was positive (speckled pattern, 1:320) and human immunodeficiency virus antibody was negative. There was an Epstein-Barr virus infection history and insufficient confirmation of other viral or fungal infections then, but anti-streptolysin O was elevated (384 IU/mL). Ultrasound showed multiple inhomogeneous occupancies in the left axilla (*Figure 1A-1C*), multiple mild lymphadenopathies (right axilla and cervix, bilateral inguen, and splenic hilar region), splenic thickening and inhomogeneous changes, and hepatomegaly. Physical examinations discovered a left axillary mass of approximately 4 centimeters in diameter with smooth border, tough texture, and average mobility. Questioning of the family revealed that the left axillary mass had been inadvertently palpated as early as 4 years ago [2017] but with no attention being paid to it. A retrospective comparison to radiographic findings 1 year ago discovered a significant enlargement of the left axillary mass and an excisional biopsy was therefore performed (July 6, 2021). Histopathological detection suggested the diagnosis of CD of the hyaline vascular (HV) subtype (*Figure 1D,1E*).

Given the absence of improved inflammatory indicators after lesion excision, positron emission tomography (PET)/CT was recommended to exclude the multicentric subtype. As expected, PET/CT demonstrated multiple involvements of CD, including LNs throughout the body, the spleen, bone and bone marrow, and the nasopharynx (*Figure 1F*) (August 3, 2021). According to the international consensus diagnostic criteria for HHV-8-negative/iMCD [2017] (3), a corrected diagnosis of HV-iMCD was established.

Treatment and outcome

Given that the inflammatory indicators had turned normal only in the early stage of methotrexate and tocilizumab treatment for CTD, rituximab (500 mg every week) in combination with prednisolone and methotrexate was applied after the diagnosis of iMCD (August 6, 2021). Unexpectedly, rituximab did not work after just four doses as inflammatory markers rebounded again. Another hospital adopted a therapy regimen of thalidomide and dexamethasone (from September 23, 2021 to July 17, 2023), during which inflammation indicators continued to fluctuate above normal values (CRP 21–62 mg/L, ESR 19–27 mm/h, IL-6 3.3–76 pg/mL). Therefore, the patient tried on siltuximab (every 3 or 4 weeks) from July 21, 2023 and received a total of 8 doses to the last follow-up visit (February 2024). Interestingly, the CRP and ESR levels were well controlled (by the family's dictation due to the unavailability of examination reports) but the IL-6 level was exceptionally high (1,277.8–4,018.28 pg/mL). The patient presented no discomfort and no difference from normal people since the diagnosis of iMCD.

The detailed clinical course is shown in *Figure 2*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was taken from the patient's guardians for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

For more information, we reviewed medical literature with the keywords "Castleman disease" and "connective tissue disorder" from 2003 to 2023 by searching medical journal databases. We identified 25 cases associated with both CD and CTD, and detailed information was summarized in Table S1.

For our patient, the most critical point was whether he actually had CTD and iMCD. It is well known that iMCD and CTD can mimic each other but no biomarker that can reliably distinguish between them has been found in the present research. Additionally, the diagnosis of both iMCD and CTD are exclusive, contributing to the controversy of the diagnosis. We, therefore, consider that the possibility that the patient suffered from only one of the two diseases

Table 1 Laboratory results upon the diagnosis of Castleman disease

Category	Index	Result	Reference
Hematology	Erythrocyte ($\times10^{12}$/L)	4.2	4.00–5.50
	Hemoglobin (g/L)	107 ↓	110–160
	Leukocyte ($\times10^{9}$/L)	10.39 ↑	4.00–10.00
	Platelet ($\times10^{9}$/L)	313	100–400
	Lymphocyte (%)	23.3 ↓	30.0–40.0
	Monocyte (%)	8.7 ↑	3.0–8.0
	Neutrophil (%)	67.5	50.0–70.0
	Eosinophil (%)	0.3	0.5–5.0
	Basophil (%)	0.2	0–1.0
Infection indicators	Anti-streptolysin O (IU/mL)	384.0 ↑	<200
	Epstein-Barr virus-DNA	Negative	Negative
	Anti-EBEA IgG (RU/mL)	194.25 ↑	<20
	Anti-EBNA IgG (RU/mL)	96.15 ↑	<20
	Anti-EBVCA IgM (RU/mL)	Negative	Negative
	Anti-EBVCA IgG (RU/mL)	>200 ↑	<20
	CMV-DNA	Negative	Negative
	Anti-CMV IgG (U/mL)	281.1 ↑	<0.5
	Anti-CMV IgM (U/mL)	Positive ↑	Negative
	HBsAg	Negative	Negative
	HCV-antibody	Negative	Negative
	HIV-antigen/antibody	Negative	Negative
Immunity	ANA 1:320	Speckled pattern ↑	Negative
	Anti-dsDNA	Negative	Negative
	Anti-SSA/SSB	Negative	Negative
	Rheumatoid factor	Negative	Negative
	Direct Coombs	Negative	Negative
	C3 (g/L)	1.72	0.67–1.76
	C4 (g/L)	0.48 ↑	0.1–0.4
	IgG (g/L)	14.20	6.98–14.26
	IgA (g/L)	1.83	0.92–2.5
	IgM (g/L)	0.81	0.56–2.16
	IgE (KU/L)	1,262.40 ↑	<100
	$CD19^{+}$ (%)	12.40 ↓	14–21
	$CD4^{+}$ (%)	51.63 ↑	29–36
	$CD8^{+}$ (%)	19.22 ↓	24–34

Table 1 (*continued*)

Table 1 (*continued*)

Category	Index	Result	Reference
Biochemistry	Total protein (g/L)	67.2	65–85
	Albumin (g/L)	34.21 ↓	40–55
	Globulin (g/L)	32.99 ↑	20–30
	AST (IU/L)	14.29 ↓	15–40
	ALT (IU/L)	6.90 ↓	9–50
	ALP (IU/L)	165.57	54–369
	Total bilirubin (μmol/L)	9.90	3.4–17.1
	γ-GGT (IU/L)	95.03 ↑	8–57
	Cholinesterase (U/L)	4,426 ↓	5,300–11,300
	Prealbumin (mg/L)	18.60 ↓	200–400
	Creatinine (μmol/L)	58.90	21–65
	Creatine kinase (IU/L)	40	0–164
	Urea (mmol/L)	2.55 ↓	2.8–7.6
	Na (mmol/L)	133.78 ↓	137–147
	K (mmol/L)	4.10	3.5–5.3
	Cl (mmol/L)	99.92	96–108
	Ca (mmol/L)	2.16 ↓	2.2–2.65
	LDH (IU/L)	221	110–290
	CRP (mg/L)	245.87 ↑	<8
	ESR (mm/h)	120 ↑	0–21
	SAA (mg/L)	>550 ↑	<10
	Procalcitonin (ng/mL)	0.55 ↑	<0.05
	Ferritin (ng/mL)	261.10 ↑	15.69–92.4
	Glucose (mmol/L)	5.11	3.9–6.1
	IL-6 (pg/mL)	11.3	<20
	IL-8 (pg/mL)	60.1 ↑	<21.4
Coagulation	D-dimer (mg/L)	0.97 ↑	0–0.5
	INR	1.28 ↑	0.8–1.2
	PT (s)	16.1 ↑	11–14.5
	PTA (%)	64.0 ↓	80–120
	APTT (s)	38.1	26–40
	TT (s)	20.1	14–21
	Fibrinogen (g/L)	7.32 ↑	2–4
	FDP (mg/L)	3.86	0–5

↓, below the normal level; ↑, above the normal level. EBEA, Epstein-Barr early antigen; IgG, immunoglobulin G; EBNA, Epstein-Barr nuclear antigen; EBVCA, Epstein-Barr virus capsid antigen; IgM, immunoglobulin M; CMV, cytomegalovirus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ANA, antinuclear antibody; SSA, Sjögren's syndrome type A; SSB, Sjögren's syndrome type B; IgA, immunoglobulin A; IgE, immunoglobulin E; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A; IL, interleukin; INR, international normalized ratio; PT, prothrombin time; PTA, prothrombin activity; APTT, activated partial thromboplastin time; TT, thrombin time; FDP, fibrin/fibrinogen degradation product.

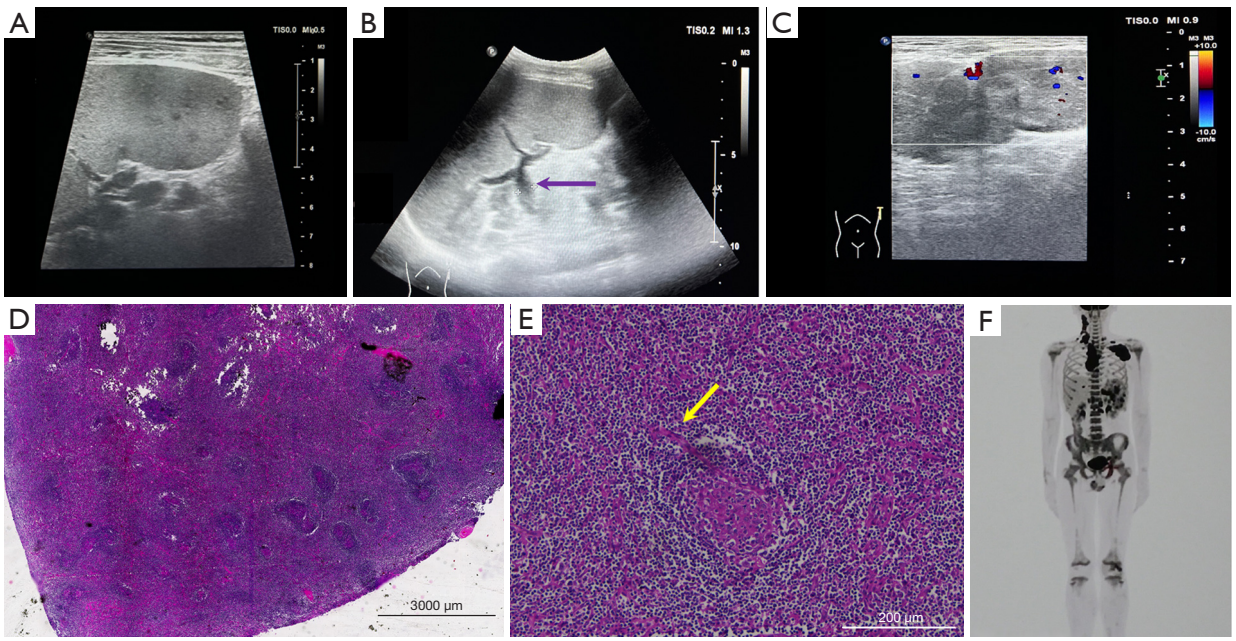

Figure 1 Imaging and histopathological findings. (A) Ultrasound showed multiple oval inhomogeneous and hypoechoic regions in the left axilla, partially arranged in strings. (B) Ultrasound showed thick blood vessels passing through the mass (purple arrow). (C) Color Doppler flow imaging detected blood flow signals in the mass. (D) Biopsy of the left axillary mass showed increased numbers of lymphoid follicles, and regressed germinal centers (hematoxylin-eosin staining). (E) A regressed germinal center was penetrated by a hyaline blood vessel (yellow arrow) (hematoxylin-eosin staining). (F) PET-CT showed the multiple involvement of Castleman disease. PET, positron emission tomography; CT, computed tomography.

or both cannot be excluded at this time. The initial left axillary LN enlargement originated from which disease was also ambiguous because of the late excisional biopsy, resulting in the order of presentation of the two diseases remaining unclear. Further clarification of the unique and shared pathophysiologic mechanisms may be beneficial.

CD and CTD have a range of overlapping presentations. Almost all cases as recorded in the literature, including the case of our patient, presented with enlarged LNs, abnormal laboratory indicators, positive autoantibodies or direct Coombs test, and systemic symptoms. Since the shared multisystemic nature of both, compared to cases with CD alone, it is more likely to affect other organs when combined with CTD. Skin, kidneys, and osteoarticular system are most vulnerable, and liver damage, peripheral polyneuropathy, and central nervous system impairment can appear in rare cases (Table S1). Another retrospective study observed a greater tendency for skin/mucosal damage and pulmonary complications in CD with concomitant autoimmune disease (5). It is noteworthy that the clinical presentations, MRI features, and bone biopsy findings of our patient did not allow the exclusion of CRMO, an autoimmune disease commonly seen in children and adolescents. To our knowledge, no cases of CD combined with CRMO have been reported to date. Methotrexate is one of the treatment arms recommended by the recent expert consensus (6), and the patient showed significant improvement in the technetium bone scan findings after about 1 year of methotrexate treatment. Whole-body MRI is more recommended than technetium bone scan for the evaluation of CRMO in children due to the harmfulness of radiation, in which the most typical presentation is increased signal on T2-weighted images (7).

PET/CT is an invaluable tool to help identify the multicentric phenotype of CD, but the issue is that the unaffordability, unpopularity, and the existence of exceptions limit the clinical application to some extent. In particular, in our case, the maximum standardized uptake value (SUVmax) of LNs was significantly higher than that of other involved organs (20.3 *vs.* 7.7, P=0.004). However, the average level of SUVmax in the LNs of patients with CD is 4.4 (8), while the value is 4 in patients with rheumatoid arthritis (9),

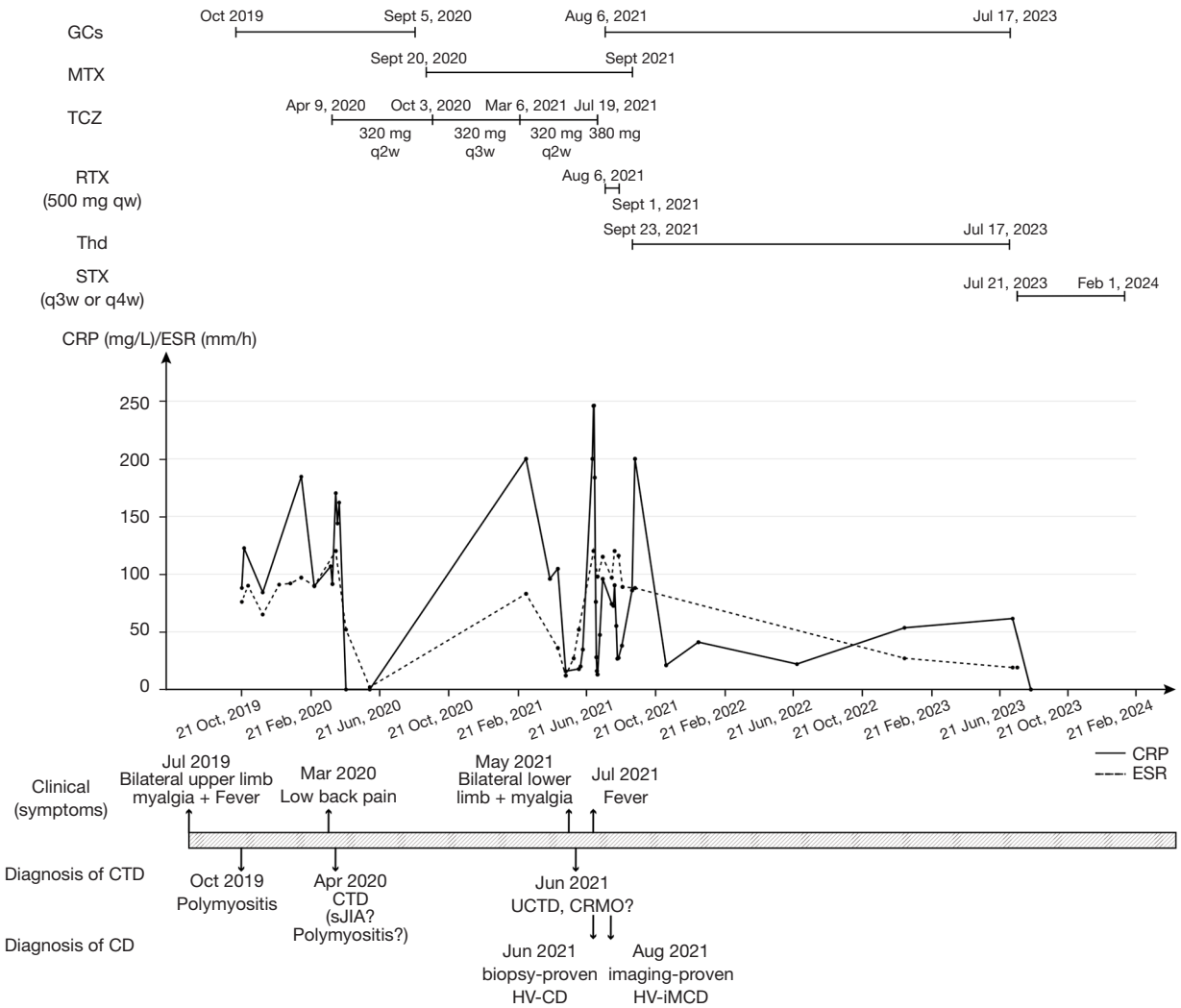

Figure 2 Clinical course. GCs, glucocorticoids; MTX, methotrexate; TCZ, tocilizumab; RTX, rituximab; Thd, thalidomide; STX, siltuximab; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CTD, connective tissue disorder; sJIA, systemic juvenile idiopathic arthritis; UCTD, undifferentiated connective tissue disorder; CRMO, chronic recurrent multifocal osteomyelitis; CD, Castleman disease; HV, hyaline vascular; iMCD, idiopathic multicentric Castleman disease.

5.55 in patients with adult-onset Still's disease (10), and 3.5–5.6 in SS (11). It seems that the identification of CD and CTD by SUVmax is unreliable and still depends on histopathological results.

There has been no agreement on the mechanism by which CD and CTD exist in the same patient. The crucial function of IL-6 in the pathogenesis of iMCD was proposed about 30 years ago (12), which is to blame for the production of large amounts of autoantibodies by inducing B cells to proliferate and mature into plasma cells (2). More IL-6 creation is further stimulated by the abnormal immune response due to excess autoantibodies (13), forming a humoral immune feedback loop that leads to the development and progression of CD and CTD. C-X-C motif chemokine ligand 13 (CXCL13) was identified as the most upregulated chemokine during the flare phase of iMCD, and proven as the driving chemokine for iMCD-like inflammation by constructing patient-derived xenograft models (14). Meanwhile, emerging studies demonstrated that the CXCL13 signal pathway is involved in the pathogenesis of various autoimmune diseases by promoting ectopic lymphoid neogenesis, regulating lymphocyte function,

and inducing proinflammatory cytokines (15). In addition, patients with CD accompanied by CTD presented a lower proportion of T cells and a higher proportion of nature killer cells (5), suggesting that dysregulation of cellular and innate immunity are also involved in disease evolution.

IL-6-block therapy plays an essential role in both CTD and iMCD and has been approved as first-line treatment for iMCD (3). Tocilizumab and siltuximab are both IL6-block monoclonal antibodies, targeting IL-6R and IL-6 respectively. Interestingly, only siltuximab was effective in controlling inflammation in our patient, but the current study has not revealed the mechanisms of the different responses. Although a substantial increase in IL-6 occurred after treatment, it may be a pseudo-elevation caused by the presence of siltuximab-IL-6 complexes (16). High IgG and fibrinogen levels before treatment and a 17% reduction in CXCL13 by 8 days after therapy have been identified as predictive indicators of siltuximab response (17,18). We look forward to more response prediction models for different therapies so that patients can be given treatments more in time.

Conclusions

In this study, we report a pediatric case diagnosed with CTD and iMCD. He presented with stable clinical state after regular treatment and his uncontrolled inflammation was eventually normalized by siltuximab. It took about 3 years to find the most effective therapy which is a result of a combination of diagnostic ambiguity and response predicting difficulty. Therefore, the pathophysiological mechanism of CD and CTD coexistence and treatment response predicting models remain to be explored so as to improve the efficiency of diagnosis and treatment.

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Footnote

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Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-605/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-605/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. We confirm that all figures and tables in this manuscript are original. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's guardians for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Supplementary

Table S1 Case reports of patients with CD and CTD described in the literature

Reference	Age (years)/ sex	CD	CTD	Interval (CD-CTD)	Antibodies	Overlapping abnormalities							Therapy
						LAP	Systematic symptoms	Hepatomegaly/ splenomegaly	Abnormal inflammatory markers	Thrombocytopenia/ thrombocytosis	Serum protein	Multiple systems involvement	
Ma *et al.* 2023 (19)	12/F	HV-UCD	SLE	0	ANA (+), anti-dsDNA (+), anti-Ro (+), anti-nucleosome (+), anticardiolipin (+)	Cervix	Fluid accumulation, weight loss, anemia (Hb 64.2 g/L)	Splenomegaly	CRP (25.2 mg/L), ESR (94 mm/h), ferritin (685 ng/mL)	Thrombocytopenia (71×10^9/L)	Hyper γ (IgG 28.6 g/L)	Skin lesions, osteoporosis, finger flexion and deformity, arthralgia	Surgery, prednisone acetate, hydroxychloroquine sulfate, leflunomide, thalidomide
Khabbazi *et al.* 2023 (20)	39/F	HV-MCD	SLE	18 years	ANA (179 IU/mL)	Axilla, cervix	Fever, fluid accumulation, anemia (Hb 117 g/L)	–	Leukocyte (21.5×10^9/L), CRP (19 mg/L), ESR (80 mm/h)	–	Hypo ALB (33 g/L)	Skin lesions	Prednisolone, hydroxychloroquine
Watanabe *et al.* 2023 (21)	60/M	iMCD-TAFRO	SS	0	ANA 1:40, anti-SSA (1,200 U/mL), anti-SSB (93.1 U/mL)	Cervix, chest	Fever, fluid accumulation	–	Hyperleukocytosis, CRP (184 mg/L), elevated IL-2, IL-6, VEGF	Thrombocytopenia (87×10^9/L)	Hypo ALB, hyper γ (IgG 21.5 g/L)	Renal dysfunction	Corticosteroid, tocilizumab, immunoglobulin, rituximab, belimumab
Okyar *et al.* 2023 (22)	73/F	HV-iMCD-TAFRO	SLE	0	ANA (>1:80), anti-dsDNA (+), anti-Sm (+), direct Coombs (+), RF (49 IU/mL), C3 (0.4 g/L), C4 (0.14 g/L)	Left axilla	Fever, weight loss, malaise, fluid accumulation, anemia (Hb 93 g/L)	Hepatomegaly	CRP (75 mg/L), ESR (49 mm/h)	Thrombocytopenia (0.2×10^9/L)	–	Skin lesions, arthritis	Prednisolone, hydroxychloroquine, azathioprine
Viallard *et al.* 2022 (23)	37/NA	PC-iMCD	SLE	10 years	anti-dsDNA (177 IU/mL), anti-SSA (+)	Axilla, cervix, groin, retroperitoneum	Fever, weight loss	–	CRP (12 mg/L)	–	Polyclonal hyper γ	Skin lesions	Hydroxychloroquine, thalidomide, corticosteroid, mycophenolate mofetil
Ono *et al.* 2021 (24)	43/M	Mix-iMCD-TAFRO	panniculitis	0	C3 (0.38 g/L), C4 (0.067 g/L)	Cervix, chest, abdomen	Fever, fatigue, fluid accumulation	–	Leukocyte (15.6×10^9/L), CRP (274 mg/L), IL-6 (46.7 pg/mL), VEGF (852 pg/mL)	Thrombocytopenia (down to 50×10^9/L)	–	Liver damage, acute kidney injury, adrenal lesions	Corticosteroids, cyclosporine, tocilizumab
Demirkan *et al.* 2021 (25)	16/F	UCD	SLE	0	anti-dsDNA (169.6 IU/mL), anti-Sm (+++), ANA (1:1,000), C3 (0.48 g/L), C4 (0.03 g/L)	Abdomen	Anemia (Hb 109 g/L)	Hepatomegaly, splenomegaly	CRP (11.05 mg/L), ESR (52 mm/h)	–	–	Arthritis	Surgery, prednisolone, hydroxychloroquine
Popovic Dragonjic *et al.* 2020 (26)	39/M	POEMS-MCD	MCTD	0	ANA (6.7 U/mL), anti-RNP 70 (>200 U/mL)	Bilateral groin, mediastinum	Fever, weight loss, fluid accumulation, anemia (Hb 91 g/L)	Hepatomegaly, splenomegaly	Leukocyte (14.9×10^9/L), CRP (118 mg/L), PCT (0.13 ng/mL), IL-6 (12.23 pg/mL)	Thrombocytosis (736×10^9/L)	Hypo ALB (25 g/L), polyclonal hyper γ (20.8%)	Skin lesions, polyneuropathy, central nervous system effect	Prednisone
Pan *et al.* 2020 (27)	45/F	iMCD	SS	0	ANA 1:320, anti-SSA (+), anti-SSB (+)	Mediastinum, subclavian, bilateral axilla, groin	Fever, weight loss, fluid accumulation	–	CRP (15.9 mg/L), ESR (50 mm/h), IL-6 (4,601 pg/mL)	–	Hypo ALB (25.2 g/L), hyper γ (IgG 22.1 g/L)	Secondary membranous nephropathy	Tocilizumab, methylprednisolone, cyclophosphamide
Soudet *et al.* 2018 (28)	44/F	PC-iMCD	SS	0	–	Axilla, groin, maxilla	Fever, night sweats, anemia (Hb 84 g/L)	–	CRP (150 mg/L)	–	Hypo ALB (26 g/L), hyper γ (IgM kappa 8.8 g/L)	Skin lesions, bone lytic lesions	Anakinra
Dei-Adomakoh *et al.* 2018 (29)	34/F	PC-iMCD	SS	0	–	Submandibular	Fluid accumulation, sweats, anemia (Hb 89 g/L)	–	CRP (206 mg/L), ESR (98 mm/h)	–	–	–	R-CHOP, chlorambucil, rituximab
Zhang *et al.* 2015 (30)	44/M	HV-MCD	SLE	0	ANA (1:160), anti-dsDNA (+), anti-SSA (+), reduced complement levels	Axilla, cervix, groin, mediastinum, retroperitoneum	Fever, weight loss, night sweats, fluid accumulation, anemia (Hb 89 g/L)	Hepatomegaly, splenomegaly	ESR (35 mm/h)	Thrombocytopenia (9×10^9/L)	Hypo ALB (27 g/L), hyper γ (IgG 19.3 g/L)	Kidney dysfunction, arthralgia	CHOP, immunoglobulin, steroids, danazol, thrombopoietin, rituximab, RCOP
Gracia-Cazaña *et al.* 2015 (31)	49/M	iMCD	MCTD	0	ANA (1:1,280), anti-Sm (+), anti-U1RNP (+)	–	Fluid accumulation	–	–	–	–	Skin lesions, muscle weakness, polyneuropathy	Corticosteroids, antimalarial drugs, rituximab, methylprednisolone
Oyaert *et al.* 2014 (32)	44/F	PC-iMCD	SLE	30 years	ANA (+), ENA (+), direct Coombs (+)	Mediastinum, abdomen, groin	Weight loss, fatigue, night sweats	–	CRP (19 mg/L), ESR (49 mm/h)	Thrombocytosis (452×10^9/L)	Hypo ALB, hyper γ (IgG 23 g/L)	–	Rituximab, R-CHOP, methylprednisolone
Motegi *et al.* 2013 (33)	62/F	HV-MCD	systemic sclerosis	–8 years	anti-SSA (+)	Axilla, cervix, groin, abdomen	Fluid accumulation	Splenomegaly	IL-6 (8.4 pg/mL)	–	Hyper γ	Skin lesions (sclerosis), calcinosis	Prednisolone
Hu *et al.* 2013 (34)	16/M	HV-MCD	SLE	–3 years	ANA (1:160), C3 (0.28 g/L), anti-dsDNA (787 IU/mL)	Axilla, cervix, groin	Fever	–	CRP (10.9 mg/L)	–	–	Skin lesions, kidney dysfunction	Fludarabine, cholera toxin, prednisone
Kerr *et al.* 2012 (35)	46/F	HV-iMCD	RA, SS	11 years	RF (78.5 IU/mL), anti-CCP (+), ANA (+), anti-SSA (+), anti-SSB (+)	Axilla, cervix, mediastinum, supraclavicular, groin	Weight loss, anemia (Hb 83 g/L)	Splenomegaly	CRP (39 mg/L), ESR (>140 mm/h)	–	Hypo ALB (30 g/L), polyclonal hyper γ	Skin lesions, arthritis	Sulfasalazine, hydroxychloroquine, methotrexate, rituximab
Xia *et al.* 2012 (36)	23/F	CD	SLE	0	ANA (1:320), anti-dsDNA (+), RF (27.3 IU/mL)	Axilla, cervix, infraclavicular, groin	Fever, weight loss, sweats, fatigue, fluid accumulation, anemia (Hb 90 g/L)	–	CRP (32.2 mg/L), ESR (130 mm/h)	–	Hypo ALB (3.08 g/L)	Skin lesions	Prednisolone
Charli-Joseph *et al.* 2011 (37)	31/F	MCD	SS	–1 year	–	Generalized LAP	Fever, weight loss, fluid accumulation, anemia (Hb 96 g/L)	Hepatomegaly, splenomegaly	–	–	–	Skin lesions, arthralgia, polyneuropathy, chronic renal disease	Immunosuppressor, prednisone
Rice *et al.* 2011 (38)	37/F	HV-UCD	sarcoidosis	0	–	Cervix	Unknown	–	–	–	–	–	Prednisone, methotrexate
Chrispal *et al.* 2010 (39)	16/F	HV-CD	MCTD	0	ANA (+), RF (+), direct Coombs (+), anti-U1RNP (136 U/mL), reduced complement levels	Mediastinum	Fever, fluid accumulation	–	–	–	Hypo ALB	Skin lesions, arthritis, nephrotic syndrome	Prednisolone, azathioprine, hydroxychloroquine
Yuri *et al.* 2008 (40)	64/F	HV-POEMS-MCD	SS	0	anti-SSA (+), anti-SSB (+)	Cervix	Fluid accumulation	–	–	–	–	Skin lesions, polyneuropathy	Prednisolone
Jacobs *et al.* 2007 (41)	66/F	HHV8-MCD	RA	NA	–	Axilla, mediastinum, retroperitoneum	Fever, fatigue, weight loss, night sweats, asthenia, anorexia, anemia (Hb 106 g/L)	Splenomegaly	ESR (100 mm/h)	–	–	–	Prednisone, methotrexate
Van de Voorde *et al.* 2004 (42)	21/F	MCD	SLE	8 weeks	Direct Coombs (+), ANA (+), Lupus anticoagulant (+), anti-SSA (1:640), decreased C3, C4	Cervix	Fever, weight loss, fatigue, fluid accumulation, anemia (Hb 84 g/L)	Hepatomegaly, splenomegaly	Leukocyte (15.3×10^9/L), CRP (284 mg/L), ESR (53 mm/h)	–	–	Arthritis, renal dysfunction	Prednisolone, CHOP, rituximab, glucocorticoids, methotrexate, cyclosporine
De Marchi *et al.* 2004 (43)	19/F	Mix-MCD	MCTD	7 years	ANA (+), ENA (+), direct Coombs (+), anti-platelets (+), anticardiolipin (+), Lupus anticoagulant (+)	Axilla, cervix, groin, abdomen, mediastinum	Fever, fluid accumulation, anemia (Hb 75.4 g/L)	Hepatomegaly, splenomegaly	Leukocyte (10.1×10^9/L), CRP (23.4 mg/L), ESR (115 mm/h)	Thrombocytopenia (98×10^9/L)	Hypo ALB (24 g/L), hyper γ (IgG 17.2 g/L)	Arthritis, acute renal failure, nephrotic syndrome	Glucocorticoid, methotrexate, cyclosporine A, IVIG, CHOP, azathioprine

CD, Castleman disease; CTD, connective tissue disorder; LAP, lymphadenopathy; F, female; HV, hyaline vascular; MCD, multicentric CD; SLE, systemic lupus erythematosus; Hb, hemoglobin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; hypo ALB, hypoalbuminemia; M, male; iMCD, idiopathic MCD; TAFRO, thrombocytopenia, anasarca/ascites, reticulin fibrosis in bone marrow, renal dysfunction, organomegaly; SS, Sjögren's syndrome; IL, interleukin; VEGF, vascular endothelial growth factor; hyper γ, hypergammaglobulinemia; RF, rheumatoid factor; PC, plasma cell; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes; MCTD, mixed CTD; PCT, procalcitonin; UCD, unicentric CD; R-CHOP, rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone; RA, rheumatoid arthritis; HHV-8, human herpes virus-8.

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