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REVIEW

Multicentric Castleman's Disease: A Challenging Diagnosis

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Abstract Multicentric Castleman's disease (MCD) is a sytemic disorder with flares of non-specific symptoms suggestive of a chronic inflammatory syndrome. It is typically accompanied by generalized lymphadenopathy and multiorgan involvement. Histologically, two main variants of Castleman's disease exist, the hyalin vascular type and the plasma cell variant. Upon localization unicentric (localized), and multicentric (diffuse, systemic) subtypes can be distinguished with more different disease outcomes. Patients often exhibit acute phase reactions and several autoimmune phenomena, and are at high risk for developing malignancies. Both the idiopathic and the HHV-8-driven infectious forms of MCD represent distinct disease entities with a less favorable prognosis. The induction of human IL-6 excess via yet unknown upstream mechanisms, and overexpression of viral IL-6 by HHV-8 can pivotally influence MCD biology. Based on the role of IL-6 in pathogenesis, MCD is also designated as IL-6 lymphadenopathy. To date there are no direct therapeutic evidences, but having been translated to daily practice the main regulatory factors may serve as promising therapeutic targets.

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Introduction

Castleman's disease (CD, or angiofollicular lymph node hyperplasia) represents an atypical, indolent, heterogeneous, non-clonal lymphoproliferative disorder with unclear etiology. In 1956 Benjamin Castleman described this unusual condition in a series of 13 patients [1]. CD patients of different ages and cases have been reported from adolescence into the seventh/eighth decade with a mild male predominance, however there are no reliable data correctly estimating CD incidence and prevalence [2, 3]. Histologically, two main variants of CD exist, a hyaline vascular type, (HV) and a plasma cell variant (PC), and occasionally a third mixed, uncommon form, the hyaline vascular-plasma cell (HVP) variant [2, 4]. Considering the localisation, CD can be separated into unicentric (localized) and multicentric (diffuse, systemic) subtypes with different disease outcomes [2, 5, 6]. Clinically, several subgroups of CD are further distinguishable, including a unicentric HV form found appr. in 70–80 % of cases, a localized PC type accounting for 15–20 %, a rare localized mixed form, a multicentric PC variant identified appr. in 10 %, and the infrequent multisystemic HV and mixed types [7, 8]. The clinical course of CD is fairly variable. Patients with the hyaline vascular (mostly localized) variant may exhibit no symptoms or only lymphadenopathy while those with the multicentric, more aggressive plasma cell type typically present with fever, night sweats, weight loss, generalized peripheral lymphadenopathy and/or widespread systemic lymphadenopathy, and multiorgan involvement [4, 6]. Multicentric CD (MCD) is more likely accompanied by acute phase reactions and several autoimmune features [9, 10]. Since lymphadenopathy

and autoantibodies are usually present in systemic autoimmune diseases, a clear distinction among the different disease entities is uncertain. The pleiotropic cytokine IL-6 has been found to play a pivotal role in MCD pathogenesis, therefore a new designation for the disease, i.e. IL-6 lymphadenopathy has been proposed [10]. Chronic HIV carriers are primarily affected by MCD, though the disorder could be manifestated in HIV-negative patients as well, who are usually older or in a somehow immunocompromised state [11]. Further, a strict association of MCD with HHV-8 coinfection has also been documented [12]. HHV-8-related MCD probably may result from errors of T cell immunity. In addition to idiopathic MCD the HHV-8-driven infectious form represents a distinct disease entity [13]. Unlike localized CD the prognosis for the MCD PC variant is generally worse [6, 7, 9]. Moreover, some MCD cases are associated with malignancies, especially with Kaposi's sarcoma and/or different lymphomas, and POEMS syndrome (**p**olyneuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**onoclonal gammopathy, **s**kin abnormalities) [6, 7]. To date there are no direct therapeutic evidences.

Multicentric Castleman's Disease

Around 10 % of all CD cases are present as MCD, usually of the plasma cell variant [2, 4] (Fig. 1). First described in 1978 MCD is a sytemic disorder with flares of non-specific symptoms like fevers, night sweats, weight loss, malaise, weakness and fatigue suggestive of a chronic inflammatory syndrome [5]. Patients often exhibit acute phase reaction and several autoimmune phenomena [9, 10]. MCD is typically accompanied by generalized peripheral and visceral lymphadenopathy, and multiorgan involvement [4, 6]. Within the spectrum of extranodal manifestations patients frequently display hepatosplenomegaly, but less commonly

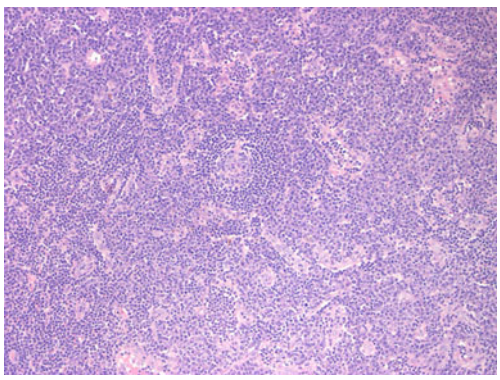

Fig. 1 Microscopic examination of an axillary lymph node indicating typical features of plasma cell type Castleman's disease (abundant follicular hyperplasia with altered nodal architecture, involuted germinal centers surrounded by a widened mantle zone, and a heavy infiltrate of polyclonal plasma cells in the interfollicular area) (H&E, x10)

kidneys, lungs, nervous system, joints, skin, or endocrine glands are also affected [8, 14]. Renal complications are occasional, thus limited cases of renal amyloidosis, various types of glomerulonephritides, interstitial nephritis, and thrombotic microangiopathy have been reported [15, 16]. Pulmonary involvement can present as non-infectious interstitial lymphoid infiltrates mainly among HIV-infected MCD patients [9, 10, 17].

There is a moderate male predominance with a median age of the fifth-sixth decade. HIV-positive persons are much prone to develop MCD at a younger age and co-infection with human herpesvirus-8 (HHV-8, also known as Kaposi's sarcoma-associated herpesvirus) [11, 12]. Although the natural history of MCD is unpredictable, different disease progression patterns have been found: an aggressive rapidly fatal course is common in HIV-positive patients; a slowly progressive chronic course with indolent onset and sustained symptoms may persist without worsening for a while; and an episodic relapsing "waxing and waning" course with exacerbations and spontaneous remissions occurs more frequently [9, 18].

Disease Outcome

The outcome of MCD potentially can be fatal not only due to multiorgan failure or fulminant infections but patients are at high risk for developing non-Hodgkin (NHL) and Hodgkin lymphomas, Kaposi's sarcoma, and POEMS syndrome, especially in the HHV-8-related forms [6, 7, 9]. The appearance of HHV-8 in lymph nodes of HIV-infected MCD patients is almost universal, though HHV-8 can be detected in appr. 40 % of HIV-negative cases as well [12, 19, 20]. During their clinical course up to 70 % of HIV-positive MCD persons and appr. 10 % of the HIV-negative ones will presented with Kaposi's sarcoma [21]. In addition to HIV-infection there is an appr. 15-fold increase in lymphoma risk among HHV-8-coinfected MCD patients since the originally polyclonal lymphoplasmacytic proliferation may escape control and progress into clonal malignant transformation [22]. NHLs arising in HHV-8-associated MCD are EBV-negative diffuse large B-cell lymphomas, or a frank plasmablastic lymphoma [23–25].

Diagnosis of the Disease

For establishing the diagnosis of MCD thorough analysis of medical history and clinical findings, and careful histologic evaluations are essential. Nevertheless, numerous atypical lymphoproliferative disorders of various origin may exhibit some histopathologic and clinical similarities with the relatively rare idiopathic and HHV-8-related MCD therefore prudent differential diagnosis is warranted [26]. In general, the lymph node histologic abnormalities are resembling those associated with an exaggerated immune activation to

an antigenic challenge. It is important to differentiate autoimmune disease-associated lymphadenopathy, congenital immunodeficiency-associated lymphadenopathy, HIV-related lymphadenopathy, idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia (IPL), POEMS syndrome (Crow-Fukake disease), and types of malignant lymphomas [27–30]. Among systemic autoimmune diseases systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome can more likely mimic MCD [27, 31]. However, it is difficult to ascertain the opposite situations as well, when MCD performs characteristics of autoimmune diseases by displaying overlapping clinical phenotypes and several autoantibodies, or mimics a scale of currently ill-defined benign or malignant adenopathies, infectious or inflammatory conditions [26, 32, 33]. The clinical suspicion for MCD is heightened by the presence of other factors, such as HIV or HHV-8 infection. Overall, MCD can be considered as a great "imitator" making itself intricate to be diagnosed and so often missed [33, 34].

Disease Pathophysiology

The pathophysiology of MCD has not been fully elucidated. Currently, the putative etiologic role of the cytokine IL-6 and the virus HHV-8 is highlighted. Overexpression of IL-6 and high serum levels are universally found in MCD but the underlying mechanisms remained elusive [8, 10]. Nevertheless, dysregulated IL-6 has been implicated in the pathology of a series of autoimmune, chronic inflammatory, and lymphoproliferative disorders explaining partly their clinical resemblances [35, 36]. IL-6 is a proinflammatory cytokine with wide-ranging biologic activities, like regulation of immune responses, hepatic acute phase reactions, hematopoiesis, and bone metabolism [35]. Human IL-6 (hIL-6) stimulates the development and differentiation of B lymphocytes promoting their Ig-secretion, while induces Th2 shifting of T lymphocytes [37]. Both Th2 cytokines and polyclonal B cell stimulation may favour the generation of autoantibodies. Regardless the etiology constitutional symptoms of chronic inflammatory conditions are related to increased hepatic IL-6-mediated acute phase protein synthesis. Microcytic anemia of chronic diseases may arise from mechanisms including inhibited erythropoiesis by proinflammatory cytokines, ineffective response to erythropoietin, and altered iron metabolism. Hepcidin is considered as the key regulator hormone of iron metabolism [38]. Recently it has been postulated, that IL-6-induced hepatic hepcidin excess closely contributes the development of anemia [39]. IL-6 is secreted by several immunocompetent cells, as T/B lymphocytes, monocytes, fibroblasts, endothelial cells, but its exact sources in MCD are still questionable. Binding of IL-6 to its receptor results in activation of the JAK/STAT pathway thus promoting the transcription of key genes encoding acute phase reactant proteins [40].

The Pathogenic Role of Human Herpes Virus Type 8

HHV-8 is a lymphotropic gamma herpesvirus with oncogenic properties that has been linked to human malignancies such as Kaposi's sarcoma and primary effusion lymphoma, and further to MCD, and more recently to a new clinical inflammatory cytokine syndrome [12, 40, 41]. HHV-8 infected individuals are found worldwide, but the seroprevalence differs among different regions. It is less than 10 % in most Europe, America and Asia, appr. 10–30 % in the Mediterranean area, and over 50 % in sub-Saharan Africa [42, 43]. HHV-8 transmissions through the saliva, and by sexual contacts in endemic areas are far possible, however the blood-borne and organ transplant-related origins are still controversial [44, 45]. In general, infections are clinically silent unless an immunodeficiency arises so affected persons become prone to develop HHV-8-associated diseases [34, 46]. HHV-8-positive immunocompetent symptom-free persons mainly harbour latently infected cells, unless specific trigger factors alter the immune response, thus evoking a parallel productive lytic viral replication [34, 46]. The virus establishes lifelong latency in B cells. In addition to the cellular microenvironment, HHV-8 may transform cells via paracrine mechanisms by cytokines and growth factors detected at high levels in affected tissues [47]. Within MCD lymph nodes HHV-8 infects mainly lymphoplasmacytic cells of the mantle zone making them highly proliferative [34] (Fig. 2). These cells possess immunoblastic morphology, and variably express the CD20 molecule [24, 25]. MCD patients usually have elevated viral loads in the peripheral blood [34, 48], however some reports indicated negative detection of HHV-8-DNA in blood in 15–20 % of MCD cases despite the presence of HHV-8-DNA sequences in the lymph nodes. This situation may reflect actual differences regarding viral load [49–51]. LANA1 (latency-associated nuclear antigen) encoded by HHV-8 is present in almost all HHV-8-infected tissues, but lytic infection is also frequently found [34, 48]. Virally encoded IL-6 (vIL-6) is secreted by HHV-8-positive B cells particularly during viral

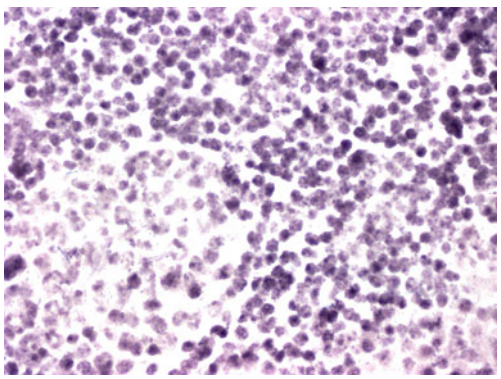

Fig. 2 In situ hybridization for HHV-8 indicates a positive nuclear reaction in a significant proportion of mantle lymphoid cells (x40)

replication, and there is only a limited gene expression in the latent phase [34, 48]. Disease progression of MCD critically depends on switches between viral latency and lytic replication, and possible lymphatic and/or hematogenous spreading [52]. Several publications have documented that HHV-8 viral load and viremia in MCD can correlate with disease activity, and sometimes predict relapse as well, especially in relation of HIV-co-infection [34, 48, 49]. Nevertheless, HHV-8 viral loads are fairly variable and may fluctuate over time, and HHV-8-DNA cannot consistently detected in different samples of infected individuals [46, 48, 49]. Further, in a subset of HHV-8-positive HIV-co-infected patients although HHV-8 latency and lytic replication occurred concomitanly, HHV-8-DNA in peripheral blood was undetectable or only low viral loads were measured [53]. vIL-6, sharing only appr. 25 % of homology with h-IL-6 can activate hIL-6 signaling pathways either via hIL-6 receptor but with a lower potency than hIL-6 does or independently of it via gp130, but in a wider variety of cells [34, 48, 54]. As a direct effect, vIL-6 can mimic several hIL-6-related functions, and enhance the level of hIL-6. Further, vIL-6 may serve as an angiogenic factor through VEGF, and favour Th2 shifting of T cell responses as well [40, 54, 55]. The B cell origin of viral- and human IL-6 are distinct. Recently HHV-8-LANA1-positive follicular dendritic cells (FDC) have also been found in lymph nodes of a proportion of HIV-infected MCD patients who had significantly higher number of CD3-positive T cells infiltrating the follicles as compared to the HHV-8-negative FDC subgroup [56]. Furthermore, among patients with HHV-8-positive FDCs there were lower numbers of HHV-8-infected mantle zone plasmablasts, in addition to decreased viral load in serum [56]. These findings indicate defective antigen presentation and T cell responses in the pathogenesis of MCD. Since angiogenesis is another important histologic co-feature of CD, the role of VEGF and EGFR is also suggested [57].

Indeed, the overexpression of vIL-6 by HHV-8, the induction of host hIL-6 excess through IL-1β/NF-κB transduction pathway by yet unknown upstream mechanisms along with the dysregulated secretion of other cytokines, like IL-10, IL-5, IL-8, IL-12, and IFNγ, and an aberrant T cell regulation all can pivotally influence MCD biology. Being translated to daily practice some of these regulatory factors may serve as promising therapeutic targets.

Therapeutic Possibilities

Several therapeutic options have been emerged in MCD with variable efficacy but there is still no consensus regarding the optimal therapy and definite recommendations. Lack of the "gold standard" is likely because of the infrequency of MCD along with its heterogenous nature, and the heterogeneity of the patients as well, and the limited available experiences. The literature is mainly confined to case reports and series, and not to comparative randomized clinical trials [8, 58]. Since the exact pathomechanism is still unknown, it is necessary to empasize, that MCD is not curable with current knowledge, therefore different treatment options are actually symptomatic and supportive with alternating longitude, and no real disease recovery can be achieved. The mainly experience-based, traditional and more recent regimens have been attempted so far include immunomanipulative options, like corticosteroids, alone or in combination with cytotoxic immunosuppression, selective/targeted immunotherapy, and biologic therapy in forms of antibodies and biologic agents, bone marrow transplantation, antiproliferative drugs, such as single-agent and combination cytoreductive chemotherapy, and antiviral agents [8, 57, 58].

Glucocorticoids have frequently used in HIV-negative MCD, although with varied average benefit. The response rate is around 60–70 % in relapsing forms, but amelioration of constitutional symptoms and inflammatory parameters usually seems to be temporary [58, 59]. Nevertheless, their administration in combination with cytotostatic drugs is certainly recommended for disease alleviation. In HIV infection, however corticosteroids can exacerbate Kaposi's sarcoma so much carefulness is required [60].

The systemic inflammatory character of MCD with immunologic disturbances and lymphoma- and autoimmune disease-like features have led to empiric trials of **cytostatic immunsuppression,** mainly along with corticosteroids, with significant but usually short-lived effectivity. The applied single-agent cytotoxic drugs include, among others azathioprine, cyclophosphamide, chlorambucil, vinca alkaloids, and bleomycin [16, 58, 61]. In HIV carriers mainly etoposide, vinblastine, and liposomal doxorubicin have produced durable MCD remission [34, 62].

Multiple combinations of **cytoreductive chemotherapy**, regularly used in treatment for NHLs have been emerged in MCD therapy as well. The protocols such as CHOP, CVP or CVAD indicated primarily for patients with an aggressive MCD and evidence of organ involvement have been found to induce remarkable disease stabilization [2, 8, 9, 18, 21, 62, 63]. Thus, in MCD polychemotherapy generally appears to be superior to monotherapy, but in HIV-infected cases cautiousness is mandatory considering the potential harmful interactions between antiretroviral and cytotoxic drugs.

Introduction of highly active anti-retroviral therapy (**HAART**) has fundamentally changed the outcome of HIV-positive MCD, especially by lowering the rate of malignant lymphoid transformation, and preventing the development of Kaposi's sarcoma [62, 64]. Conversely, in some early MCD cases with HIV infection initiation of HAART has resulted in

an aggressive MCD relapse probably due to immune reconstitution syndrome [62, 65].

Blocking the lytic replication of HHV-8 provides another rational therapeutic approach, since the clinical course of MCD especially in HIV carriers is closely related to HHV-8 viremia. In series of HIV-positive patients, however cidofovir failed to exert antiviral capacity, and foscarnet did it with controversial results [66]. Ganciclovir, and valganciclovir, in turn effectively reduced HHV-8 viral load in peripheral blood [67]. Selective targeting of HHV-8-infected plasmablasts by a combination of high-dose zidovudine and valganciclovir has also proposed [34].

Administration of **interferon-α** either alone or in combination with chemotherapy mainly was successful in inducing remission in series of patients with HIV-positive or HIV-negative MCD probably due to its broad biologic activities [21, 57]. In addition, interferon-α can be part of a consolidation therapy.

Several recent studies have indicated the clinical competency of the **anti-CD20 chimeric monoclonal antibody rituximab** in HHV-8-related MCD [68, 69]. By targeting CD20-expressing B cells rituximab via activation of ADCC or CDC, and apoptosis induction results lymphodepletion [34]. Further, the drug is supposed to decrease the number of HHV-8-positive plasmablasts and reduce IL-6 production of other B cells stimulated by the infected plasmablasts [34]. Indeed, in some studies rituximab therapy was associated with a decrease in serum IL-6 level and HHV-8 viral load [68]. Rituximab alone or in combination with corticosteroids or mono/polychemotherapy displayed mainly sufficient remission-inductive activity in both HIV-positive and HIV-negative MCD cases [68, 69]. Furthermore, following mono- or polychemotherapy rituximab should be a choice for maintaining disease stabilization. However, its use in some HIV-infected and HIV-negative, but HHV-8-positive patient with MCD was associated with worsening or reactivating of cutaneous Kaposi's sarcoma [69, 70]. To avoid this critical situation much care is advised, and in HIV carriers rituximab combination with pegylated liposomal doxorubicin is suggested.

Recently **neutralizing monoclonal antibody against IL-6R,** such as the **humanized tocilizumab** has been evaluated for MCD therapy demonstrating a rapid and profound improvement of clinical and laboratory abnormalities in series of HIV-negative and mainly HHV-8-negative patients [71–74]. Conversely, after discontinuation of treatment disease recurrence was observed, and for maintenance patients generally need prolonged drug administration [71, 72]. For Castleman's disease therapy tocilizumab was approved in Japan in 2005, but in the US and the EU however, the drug is approved for the treatment of rheumatoid arthritis only. In HHV-8-positive MCD cases only limited experiences are available on efficacy of IL-6 blocking. However, recently we have published a HIV-negative female patient diagnosed with HHV-8-positive multicentric Castleman's disease (MCD) of plasma cell type successfully treated with tocilizumab [75]. She failed to respond to combination immunosuppressive therapeutic trials of corticosteroids and azathioprine, and neither an immuno-chemotherapy of rituximab-CVP induced disease resolution. Nevertheless, the monoclonal anti-IL-6R antibody (tocilizumab) immunotherapy resulted in beneficial disease stabilization including an almost fully disappearance of extensive generalized lymphadenopathy and hepatosplenomegaly. Moreover, histologic reevaluation of a residual lymph node found preserved nodal architecture with mild polyclonal plasmacytosis without follicular hyperplasia. Another IL-6-related therapeutic approach is targeting the cytokine itself. Use of the chimeric monoclonal antibody siltuximab in patients with HIV/HHV-8-unrelated MCD has also resulted in transient resolution of disease manifestations [76].

Thalidomide is frequently chosen in treatment of plasma cell dyscrasias, particularly multiple myeloma. Like in MCD, IL-6 has a central role in disease activity of myeloma. Thalidomide was proved to downregulate IL-6 expression. Some reports have indicated its therapeutic efficacy in MCD patients resulting resolution of clinical symptoms [77]. The proteasome inhibitor **bortezomib**, which downregulates NF-κB is another drug for myeloma therapy. Two recent case reports have published on the induction of a sustained complete remission by bortezomib in refractory MCD [78, 79].

Within the cascade of proinflammatory cytokines IL-6 expression is related to the upregulation of IL-1β/NF-κB signal transduction pathway, therefore it is plausible to control IL-6 production by antagonizing IL-1β. The recombinant IL-1R antagonist **anakinra** has been found to promote disease regression in limited cases of refractory MCD [80].

Conclusions

MCD can be considered as an example for challenging diagnoses due to the many faces of the disease-related signs and symptoms along with sometimes unique clinical features. However, in cases of MCD with high mortality rate the sooner diagnosis is established the earlier appropriate therapy and possible disease stabilisation can be achieved. Regarding accurate diagnostic work up suspicion of the presence of this rare polyclonal lymphoproliferation is essential. By understanding the biology of MCD especially the central role of IL-6 and HHV-8 in the pathogenesis more promising drugs can be developed hopefully with a consensus on the optimal therapeutic strategies.

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