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CASE REPORT

Management of Castleman's Disease: Recent Advances and Case Sharing

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ABSTRACT

Castleman's disease is an uncommon lymphoproliferative disorder characterised by hyperplasia of lymphoid tissue. There are three histopathological types of Castleman's disease: hyaline vascular variant, plasma cell variant, and mixed cellularity. Hyaline vascular Castleman's disease is typically unicentric in presentation, while the plasma cell variant tends to be multicentric. Infection with human herpes virus 8 and interleukin-6 production are implicated in the pathogenesis of the disease. Unicentric Castleman's disease is often curable by surgical removal, while multicentric Castleman's disease usually manifests with constitutional symptoms and requires systemic treatment. Cytotoxic chemotherapy and / or steroids have been widely used as treatment of multicentric Castleman's disease, with varying degrees of response. The discovery of molecular components and mechanisms underlying the disease pathogenesis has been translated into targeted therapeutic approaches. Particularly, the use of anti-CD20 antibody, rituximab, antibodies targeting the interleukin-6 pathways, and antiviral agents have demonstrated efficacy in case reports and case series of multicentric Castleman's disease. In this article, we report on two patients with multicentric Castleman's disease and summarise the current understanding of the disease pathogenesis and therapeutic approaches to this complex and heterogeneous disease.

Key Words: *Antibodies, monoclonal; Giant lymph node hyperplasia; Herpesviridae; Interleukin-6; Multi-centric Castleman's disease*

中文摘要

Castleman病的治理：最新進展與病例分享

王紹明

Castleman病是一種罕見的淋巴組織增生病變，其特徵為淋巴組織腫大。Castleman病可分為三種病理類型：透明血管型、漿細胞型及混合型。Castleman病的透明血管型屬於局部型，而漿細胞型屬於多發型。發病機制與人類8型泡疹病毒感染及白介素-6（IL-6）的產生有關。局部型Castleman病通常可以手術切除治理。多發型Castleman病表現為全身症狀，需要全身性系統治療。多發型一般會使用細胞毒性化療和／或類固醇，但病人反應有很大差異。從發現Castleman病的分子成分和機制可找出針對性療法。文獻中的病例報告指出抗CD-20抗體、rituximab、抗IL-6抗體治療均對於多發型Castleman病有成效。本文報告多發型Castleman病的兩名患者，並總結對這複雜和臨床表現多樣化的疾病的病理機制及治療方法。

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INTRODUCTION

Castleman's disease (CD) is a rare lymphoproliferative disorder that was first described by Castleman and Towne in 1954 in a patient with a solitary hyperplastic mediastinal lymph node.[1] CD exhibits different histological lymph node characteristics and can be classified as a hyaline vascular variant, plasma cell variant, or mixed cellularity.[2] The hyaline vascular variant of CD is characterised by abnormal lymph follicles with regressed hyaline germinal centres and interfollicular vascular proliferation. Comparatively, CD of the plasma cell variant exhibits hyperplastic germinal centres with concentric sheets of plasma cells in the interfollicular region and lacks hyalinisation.[3]

CD can also be classified into two clinical entities based on disease presentations. The localised or unicentric type of CD (UCD) is the more common form, affecting a single lymph node or chain of lymph nodes, and is usually of hyaline vascular histology. UCD is rarely (<10%) associated with constitutional symptoms and is usually curable by lymph node resection.[4] The systemic or multicentric form of CD (MCD) is less common and mostly of the plasma cell variant. Patients with MCD have multifocal lymphadenopathy, usually accompanied by constitutional symptoms such as fever, night sweats, fatigue, weight loss, diffuse polyadenopathy, and oedema. MCD is commonly associated with laboratory abnormalities; these may include anaemia, thrombocytosis or thrombocytopaenia, leukocytosis, hypoalbuminaemia and hypergammaglobulinaemia, and increases in acute-phase proteins such as C-reactive protein, erythrocyte sedimentation rate (ESR), fibrinogen, and interleukin (IL)–6.[5] MCD can be associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome and with human immunodeficiency virus (HIV). MCD in HIV-infected patients is almost always of the mixed or plasma cell variant and is associated with human herpes virus 8 (HHV-8). HIV-associated MCD tends to run a more aggressive course, manifesting at a younger age and with prominent constitutional symptoms and generalised lymphadenopathy.[6] Patients with MCD often require systemic treatment and their prognosis is less favourable than for those with UCD.[3]

Currently, no standard treatment exists for CD. With improved understanding of the pathophysiology in recent years, new molecular targeted therapies have been added to the management options for CD with some promising outcomes. In this article, we describe two patients with MCD and discuss the management options for this rare heterogeneous condition.

CASE REPORTS

Patient 1

A 50-year-old man with good past health presented to a regional hospital in February 2003 with bilateral cervical and groin masses. The lesions had progressed over the past year and the patient reported some weight loss (5 lbs) during the same period, but was otherwise asymptomatic. Physical examination revealed multiple lymph nodes in the cervical and groin area of up to 2 cm in size. Blood counts showed mild anaemia (haemoglobin, 125 g/L [reference range, 140-175 g/L]), increased platelets (426 x 10^9 /L [reference range, 150-450 x 10^9 /L]), and normal white blood cells (10.3 x 10^9 /L [reference range, 4.5-11.0 x 10^9 /L]). The ESR was elevated (117 mm/h [reference range, 0-20 mm/h]) and the albumin/globulin ratio was reversed (31/88 g/L). No hepatosplenomegaly was detected. The patient was admitted to a medical ward for further examinations. During his hospital stay, he coincidentally contracted severe acute respiratory syndrome (SARS) at the height of the disease outbreak and was treated with ribavirin and three doses of methylprednisolone. He recovered from SARS and the lymphadenopathy also resolved.

At follow-up after three to four months, the cervical and groin lymph nodes were found to have increased in size (up to 2 cm), and blood counts revealed mild anaemia (haemoglobin, 90 g/L). Computed tomography (CT) scan showed bilateral cervical, axillary, pelvic, and groin lymphadenopathy. A biopsy of the right groin lymph nodes was performed and revealed histological patterns consistent with the plasma cell variant of CD. The patient tested negative for HIV and HHV-8. Owing to the previous response to steroids, he was treated with oral dexamethasone 40 mg daily for four days every four weeks for four cycles. The lymphadenopathy and anaemia largely resolved, and he was given dexamethasone on a pro-re-nata basis, as and when symptoms occurred over the next five years.

In 2009, the patient presented with malaise, weight loss, and progressive lymphadenopathy despite dexamethasone treatment. His treatment was switched to combination chemotherapy with cyclophosphamide, vincristine, and prednisolone (CVP) every four weeks for six cycles. The lymphadenopathy and clinical symptoms initially resolved with treatment, but recurred

after six months. He was subsequently enrolled in a clinical trial involving an anti–IL-6 antibody.

Patient 2

A 49-year-old woman presented in December 2000 with a five-month history of low-grade fever, lethargy, weight loss, and anorexia. She was anaemic (haemoglobin 68 g/L [reference range, 120-150 g/L]), had raised ESR (>100 mm/h) and alkaline phosphatase (712 U/L [reference range, 50-120 U/L]), and inverted albumin/globulin ratio (24/63 g/L). Immunoglobulin (Ig) levels showed increased IgA (5.09 g/L [reference range, 0.68-3.78 g/L]) and grossly elevated IgG (38.4 g/L [reference range, 6.94-16.18 g/L]). Ultrasound abdominal CT scan revealed enlarged intra-abdominal, para-aortic, coeliac axis, portal lymph nodes (2-3 cm in size). Positron emission tomography scan showed increased uptake in the pancreatic head and body, and left para-aortic activity, corresponding with the enlarged lymph nodes.

A bone marrow biopsy was performed and showed reactive plasmacytosis of 13% with no evidence of myeloma. Laparoscopic biopsy sections contained small pieces of lymphoid tissues covered by fibrous capsules consisting of hyperplastic follicles. There was no evidence of granulomatous inflammation, lymphoma cell infiltrate, or metastatic malignancy. Immunostains with B- and T-cell markers revealed a reactive pattern. All the findings were suggestive of MCD.

The patient was given prednisolone 40 mg daily in November 2001 and experienced prompt relief of symptoms. However, symptoms and laboratory abnormalities recurred once the prednisolone dose was reduced to 5 mg daily. Cyclosporin A 125 mg twice daily was given, but was subsequently discontinued due to lack of clinical effect and the presentation of hand tremors. The patient was then given thalidomide 100 mg daily, which controlled her symptoms for three months, but was discontinued due to increased lethargy. From November 2001 to March 2005 she received prednisolone 10 mg daily as maintenance therapy, with continuation of disease exacerbations.

In March 2005, the patient commenced rituximab therapy 375 mg/m^2 weekly for four cycles. The treatment was well tolerated and laboratory abnormalities resolved without the need for further blood transfusions. She continued with maintenance prednisolone therapy at the lower dose of 5 mg daily for the next few years. A follow-up CT scan in 2007 showed stable lymph node size. At the last follow-up in April 2012, the patient continued to be symptom free and had normal blood counts.

DISCUSSION

As CD is an uncommon, recently recognised disease, a standard approach to clinical management has not yet been established and most treatment options are based on small case series and case reports. Recent advances in the understanding of the molecular mechanisms underlying the pathophysiology of CD have provided new targets for therapeutic exploitation and led to the use of new targeted approaches to treat MCD. These have shown promising results in some patients.

Pathophysiology

Current understanding of the pathophysiology of CD suggests that the disease is mediated by the dysfunction of multiple cell signalling mechanisms involving various inflammatory mediators. One key pathway may be driven by HHV-8, which activates the IL-6–mediated pathways leading to lymphocyte proliferation and systemic manifestations of the disease.

HHV-8, also known as Kaposi's sarcoma–associated herpes virus, is detected in nearly all patients with HIV-associated CD and about 40 to 50% of those with HIV-negative CD.[7] The genome of HHV-8 encodes a number of putative proteins implicated in cell cycle regulation, apoptosis, and cytokine signalling. It has been postulated that HHV-8–infected cells can produce a viral homolog of IL-6, which binds to the human IL-6 receptor (IL-6R) and activates its downstream signalling pathways. This induces the production of vascular endothelial growth factors which, in turn, stimulate the secretion of human IL-6 by endothelial cells in the lymph nodes.[5,8]

IL-6 is a multifunctional cytokine involved in the synthesis of acute-phase reactant proteins by the liver, and is associated with development of constitutional symptoms accompanying many inflammatory diseases.[9] IL-6 can induce secretion of the peptide hormone hepcidin by the liver, leading to anaemia in chronic disease.[10] The symptoms and lymphocyte proliferation in CD are likely to be cellular events resulting from a raised IL-6 level. The underlying mechanisms for increased production of IL-6 in patients with HIV- and HHV-8–negative CD remain uncertain. There is evidence that IL-1 may be involved, since it can induce

IL-6 production through the nuclear factor-kappa B (NF-ϰB) pathway.[11]

Management Options

Treatment of CD depends on the type of disease. Surgery is the mainstay of treatment for UCD, and is usually curative for the hyaline vascular or plasma cell variants.[3] In contrast, the disseminated nature of MCD makes complete surgical excision of lymphadenopathy virtually impossible. Patients with symptomatic MCD usually require systemic treatment, and several options are available. Corticosteroids are commonly used and often result in prompt amelioration of symptoms, normalisation of laboratory parameters, and partial improvement of lymphadenopathy. However, steroid-induced remission is usually short-lived and symptoms typically recur with decreasing dose. Prolonged use of high-dose corticosteroids is associated with increased risk of infection, osteoporosis, and metabolic abnormalities.[12]

A variety of cytotoxic agents have been used for the treatment of MCD based on regimens for non-Hodgkin lymphoma. Various single-agent cytotoxic agents have been effective for some patients, and include chlorambucil, cyclophosphamide, 2-chlorodeoxyadenosine, carmustine, vincristine, and bleomycin. In particular, single-agent liposomal doxorubicin, oral etoposide, and vinblastine have been reported to produce durable remission, predominantly in HIV-infected patients.[6,13,14] Combination chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisolone and CVP have also been used and are associated with response in most patients.[15-17] Autologous stem cell transplantation has been reported to induce remission in a patient with MCD inadequately controlled by chemotherapy and corticosteroids.[18]

With the implication of HHV-8 playing a role in the pathophysiology of MCD, several case series have reported the treatment of HHV-8–associated MCD using antiviral agents that have in-vitro HHV-8 activity such as ganciclovir, foscarnet, and cidofovir; these agents have had mixed success.[19-22] The lack of response in some patients with HHV-8–associated MCD warrants further investigations through controlled trials to define the role of antiviral therapy in MCD. Highly active antiretroviral therapy may be beneficial for the treatment of HIV-associated MCD,[6,23] although MCD exacerbation may be induced at treatment initiation because of transient immune reconstitution.[24]

Additionally, some case reports describe the beneficial use of immunomodulators such as thalidomide in patients with MCD.[25-27] Thalidomide has antiangiogenic properties and may act specifically to reduce IL-6 production.[5]

Improved understanding of the molecular basis of CD has led to the trial of targeted therapies for patients with MCD. Rituximab is a monoclonal antibody to CD20 that has been effective in CD20-positive MCD patients, with or without HIV infection.[5] Durable responses were reported with rituximab as a single agent or in combination with cytotoxic chemotherapy. In a prospective study of 24 HIV-infected patients with chemotherapy-dependent MCD given rituximab once weekly for four weeks, 22 patients (92%) had sustained remission at day 60 and 17 patients (71%) had sustained remission at 1 year.[28] Rituximab treatment was well tolerated and most adverse events were mild-to-moderate in severity, and included minor exacerbations of cutaneous lesions in patients with Kaposi's sarcoma (8 of 12). Similarly, a subsequent prospective study evaluated the use of rituximab in 21 HIV-infected patients with a plasmoblastic type of MCD.[29] Fourteen patients (67%) achieved partial response and 29% had stable disease. The progression-free survival rate was 92% at one year and 79% at two years. Rituximab therapy was associated with a decline in the HHV-8 viral load, as well as in IL-10 and IL-6 levels after treatment completion.

IL-6 is now recognised as an important target in the treatment of CD and the use of monoclonal antibodies specifically targeting IL-6 or IL-6R has shown promising preclinical and clinical efficacy. Tocilizumab is a humanised monoclonal antibody against IL-6R. In a Japanese phase II study of 28 patients with HIV-associated CD who received tocilizumab infusion twice weekly for 16 weeks, treatment resulted in rapid normalisation of inflammatory parameters, alleviation of constitutional symptoms, and reduction of lymphadenopathy.[30] Tocilizumab was well tolerated and associated with adverse events of mild-to-moderate severity. Almost all patients (27 of 28) continued to receive tocilizumab for more than three years. Furthermore, 11 (73.3%) of 15 patients who had received oral corticosteroids before study entry were able to reduce the corticosteroid dose. Tocilizumab is currently approved for the treatment of CD in Japan.

More recently, siltuximab, a chimeric human-murine

monoclonal antibody that binds to and neutralises IL-6, has been investigated in a phase I study of 23 patients with HIV- and HHV-8–negative CD. The patients received siltuximab at 1-, 2-, or 3-week intervals and 18 (78%) of 23 patients achieved a clinical benefit response. Moreover, all 11 patients treated with the highest dose of siltuximab of 12 mg/kg achieved a clinical benefit response, and eight patients (73%) achieved an objective tumour response. Objective response duration ranged from 44 days to more than two years (≥889 days); one patient had complete response for ≥318 days. There was no treatment-limiting toxicity.[31] A prospective multicentre randomised phase II study is currently ongoing to further evaluate the efficacy and safety of siltuximab.

The use of bortezomib, a proteasome inhibitor, in MCD patients has shown interesting outcomes in two case reports. One report was of a 48-year-old woman with refractory HHV-8–negative MCD, who experienced complete remission for more than one year after treatment with bortezomib.[32] Additionally, a 49-year-old man with POEMS syndrome and HHV-8–negative MCD experienced sustained complete remission for more than four years after six cycles of bortezomib and dexamethasone.[33] The mechanism of action of bortezomib is likely to be through inhibition of the proteasome pathway which, in turn, inhibits the NF-κB pathway and reduces expression of pro-inflammatory proteins, including IL-6. The safety and efficacy of bortezomib in HHV-8–associated CD remain to be investigated.

CONCLUSION

Recent advances in the understanding of the pathophysiology of CD have increased insight into the key molecular players underlying the disease. Deregulated overproduction of IL-6 is pivotal in driving the disease. HHV-8 is believed to be involved in the pathophysiology of MCD through production of viral IL-6. Cytotoxic chemotherapy and / or steroids have been widely used in MCD therapy, with varying degrees of response. Insight into the molecular basis of CD has created opportunities for novel targeted therapeutic approaches. In particular, agents targeting CD20 and the IL-6 pathways were shown to be effective in treating patients with MCD. The two patients reported here demonstrate that MCD can often be refractory to conventional treatment such as steroids and / or chemotherapy, but shows marked responses to targeted agents. Further investigations, particularly controlled trials, are still needed to determine the optimal treatment combinations and provide guidance for personalised therapeutic approaches for this heterogeneous disease.

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