REVIEW ARTICLE

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healthsciences

Fifty Years of Multicentric Castleman's Disease

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Acta Oncologica Vol. 43, No. 8, pp. 698–704, 2004

Benjamin Castleman first described multicentric Castleman's disease (MCD) in a series of cases in 1954. Interest in MCD has grown in recent years following an association with human immunodeficiency virus (HIV) infection. Castleman's disease is separated into localized disease and MCD. The latter is characterized by polylymphadenopathy and multiorgan involvement. Histologically, Castleman's disease is divided into the hyalinized vascular form and a plasma cell variant, the former being more common in localized disease and the latter more common in MCD. MCD is associated with Kaposi's sarcoma herpesvirus (KSHV) infection, which is alternatively termed human herpesvirus 8 (HHV8). This virus encodes a homologue of interleukin 6 (vIL 6), which may mediate some systemic features of MCD. The diagnosis of Castleman's disease is established by biopsy and treatment is often based on published case reports only, as there are no randomized trials of therapy. Surgery has less of a role in MCD than in localized disease, but debulking by splenectomy may be useful to alleviate haematological sequelae. Systemic treatments for MCD have included chemotherapy, anti-herpesvirus treatments to reduce the KSHV viral load, highly active antiretroviral therapy (HAART) to reduce HIV viraemia and latterly monoclonal antibodies against both IL 6 and CD20. The introduction of HAART has altered the natural history of HIV infection; however, its impact on MCD is difficult to ascertain. Optimization and consensus in treatment of these patients remains a target for the future.

Received 30 March 2004
Accepted 6 September 2004

Although there is a movement to eradicate case reports and anecdotes from the medical literature, it is worth recalling that the first description of this disease appeared as a case record of the Massachusetts General Hospital, familiar to all readers of the New England Journal of Medicine, in 1954 (1). Benjamin Castleman, the pathologist at Massachusetts General Hospital, subsequently described 13 cases of localized asymptomatic mediastinal masses demonstrating lymph node hyperplasia resembling thymoma in 1956 (2). It was thought to be a non-neoplastic polyclonal lymphoproliferative disease or 'prelymphoma'. Castleman's disease has a number of descriptive synonyms including angiofollicular hyperplasia, giant cell lymph node hyperplasia and lymphoid hamartoma.

The localized form that was identified by Benjamin Castleman usually presents in young adults with localized masses in the mediastinum (60–75%), neck (20%) or less commonly intra-abdominal masses (10%). Systemic symptoms are rare with localized Castleman's disease (LCD). In contrast, multicentric Castleman's disease (MCD) presents with polylymphadenopathy and frequently multi-organ involvement and is associated with systemic features. MCD is less common than the localized variant, typically presents in the sixth decade, and follows a more aggressive natural history.

HISTOLOGY

The histology of Castleman's disease is similarly divided into two subgroups. The hyalinized vascular type is characterized by numerous small to medium-sized germinal follicles in the lymph nodes, with hyalinized vessels and a concentrically arranged mantle zone producing a characteristic 'onion peel' appearance. Hyaline vascular Castleman's disease is found in 90% of LCD but rarely in MCD and in only 3–10% of cases is it associated with systemic clinical manifestations. In contrast, the plasma cell variant is found in only 10% of patients with LCD but 80–90% of MCD. The histological appearances are of an intense plasmacytosis in the interfollicular areas of the nodes, again with a prominent increase in capillaries and post-capillary venules, which may be hyalinized. Plasma cells are identified by their clock-face nucleus and pale perinuclear cytoplasmic crescent. Mixed forms of Castleman's disease exist with both hyaline vascular and plasma cell elements present.

 ISSN 0284-186X
DOI: 10.1080/02841860410002752

VIROLOGY

With the emergence of the HIV pandemic, there has been a resurgence of interest in Castleman's disease. This followed the recognition of an association between MCD and AIDS-associated Kaposi's sarcoma (KS), again following initial publication of case reports (3). In 1994, Chang and Moore isolated a new human gammaherpesvirus from AIDS-KS lesions using differential representational analysis (4). This virus was christened with two names, Kaposi's sarcoma herpesvirus (KSHV) and human herpesvirus 8 (HHV8). The virus was rapidly associated with a number of additional pathologies including classic, allograft-associated, and endemic (African) KS variants (5, 6) and with AIDS-related primary effusion lymphomas (PEL) (7) and a range of post-transplant conditions such as bone marrow failure (8–10).

Even in the early 1980s, with the increasing emergence of the AIDS epidemic, clinicians recognized an association between Kaposi's sarcoma and MCD, observing that the two diseases frequently coexisted (3, 11, 12). Indeed, 75% of HIV-positive patients and 13% of HIV-negative patients with MCD have or will develop Kaposi's sarcoma during the course of their disease (13).

The first study that linked the aetiology and pathophysiology of MCD with KSHV was reported in 1995, just one year after the discovery of this virus. In a series of 31 patients with MCD, the virus was detected in samples from 14/14 HIV-positive patients including five patients without Kaposi's sarcoma and in 7/17 (41%) HIV-negative patients with MCD, including one case associated with cutaneous Kaposi's sarcoma. By way of controls, KSHV was detected in one of 51 HIV negative reactive lymph nodes and three of 17 HIV positive reactive lymph nodes (14). Immunohistochemical studies demonstrated that KSHV is found in the plasmablasts within MCD lesions and these cells appear to be absent from KSHV-negative MCD (15, 16). These plasmablasts have germ line immunoglobulin genes but are lambda light chain restricted and appear to represent pre-germinal centre naïve B cells that are polyclonal but monotypic (17, 18). KSHV is also present in the malignant cells of plasmablastic lymphomas that occur more frequently in patients with MCD (18, 19).

It was believed that the presence of KSHV was an omnipresent finding in HIV-associated MCD; however, the first case report of MCD in an HIV-positive individual with undetectable KSHV based on PCR and immunohistochemistry was reported last year (20). This finding needs to be confirmed as it may lead to a reinterpretation of the aetiopathogenesis of HIV associated MCD.

ROLE OF INTERKEUKIN 6

It is postulated that the mechanism of lymphoproliferation in MCD is mediated by IL-6, a pleiotropic cytokine involved in the acute phase inflammatory reaction. Human hIL-6 acts as a B-cell stimulatory factor and mediates B-cell differentiation as well as promoting the growth of B-cell malignancies (21). KSHV encodes a viral homologue of IL-6 (vIL-6) that is an early lytic antigen. KSHV-encoded vIL-6 can stimulate the known hIL-6-induced signalling pathways via the shared cytokine signalling receptor gp130 that is coupled to the endogenous JAK/STAT pathway, although there are subtle differences in the receptor activating signalling complex between the human and viral homologues (22–26).

Studies in mice and human cell lines have shown that viral encoded vIL-6 supports their growth and survival in vitro in a similar manner to hIL-6. In mice, recombinant vIL-6 induced a marked plasmacytosis similar to that found in MCD, as well as accelerating haemopoesis and inducing vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine (27). Furthermore, in MCD, a high HHV8 viral load and high levels of IL-6, IL-10, and C-reactive protein are associated with a more aggressive disease course, suggesting that both cytokines maybe involved in the pathogenesis of this disease (28). Certainly, recent data have shown that vIL-6 can induce mitogenic effects on primary Kaposi's sarcoma cells with the production of acute phase proteins that may cause localized tissue damage and attract more inflammatory cells, thereby inducing a more aggressive phenotype (29). It is intriguing that PEL cell lines are dependent on vIL6 but not hIL6, despite the lack of differences in downstream signalling. In a series of elegant experiments, this was shown to be due to subtle differences in receptor transduction that enabled vIL6 to inhibit interferon signalling that could not be achieved by hIL6 (30).

The clonality of MCD and its progression to lymphoma is also influenced by the KSHV virus. Using monoclonal antibodies to the latent nuclear antigen (LANA), KSHV has been detected in the large mantle zone plasmablasts of MCD (31). These plasmablasts expressed high levels of lambda chain restricted IgM; however, in the interfolliclular region the mature B cells were KSHV negative, IgM negative, and were polytypic. These KSHV-positive, IgM lambda restricted plasmablasts are often isolated cells but they may coalesce into microscopic aggregates known as microlymphomas and in some cases form frank plasmablastic lymphomas. The clonality of plasmablasts in 13 cases of MCD including 8 with microlymphomas and 2 with plasmablastic lymphomas has been evaluated by Ig gene rearrangement studies and revealed that the KSHV-positive plasmablasts were polyclonal in the MCD-involved lymphoid tissue and in 6 out of 8 microlymphomas. In two cases of the microlymphomas and two plasmablastic lymphomas, the KSHV-positive plasmablasts were monoclonal (18). Moreover, the absence of somatic Ig gene rearrangements suggests that the KSHV-positive

plasmablasts are derived from naïve B cells. KSHV-encoded vIL-6 was detected in only 10–15% of KSHV-positive plasmablasts but the hIL-6 receptor was expressed by all KSHV-positive plasmablasts. It is hypothesized that activation of the IL-6 signalling pathway by KSHV v1L-6 may transform naïve B cells into plasmablasts and lead to the lymphoproliferative diseases associated with this virus including MCD. These findings contrast with a recent publication describing seven patients from China with localized hyaline vascular Castleman's disease and paraneoplastic pemphigus. These tumours appeared to be monoclonal and all expressed similar IgV_H complementary determining region 3 (32).

CLINICAL

In general, MCD presents in the fourth or fifth decade of life but occurs at younger ages in people who are HIV positive. Patients often present with generalized malaise, night sweats, rigors, fever, anorexia, and weight loss. On examination, they have multiple lymphadenopathy, hepatosplenomegaly, ascites, oedema, and effusions both pulmonary and pericardial. Laboratory investigations may reveal thrombocytopaenia, anaemia hypoalbuminaemia, and hypergammaglobulinaemia. The systemic symptoms are attributed to vIL-6 and can be severe enough to cause pancytopaenia and organ failure (particularly respiratory and renal), as well as shock requiring admission into an intensive care unit. HIV-infected patients with MCD have a greater preponderance of pulmonary complications. MCD is more likely to lead to neuropathic complications than locally confined Castleman's disease. Patients can develop polyneuropathies, leptomeningeal and CNS infiltration, as well as myasthenia gravis (33). The polyneuropathy is a chronic inflammatory demyelinating neuropathy and may present as part of the rare POEMS syndrome (Crow–Fukase disease). POEMS syndrome consists of polyneuropathy, organomegaly, endocrinopathy monoclonal gammopathy, and skin changes. Patients are diagnosed with POEMS syndrome if they have two of these clinical features as well as plasma cell dyscrasia.

Not only is MCD itself potentially fatal due to organ failure but it is also associated with an increased incidence of non-Hodgkin's lymphoma (NHL). In a prospective study of 60 HIV-infected individuals with MCD, 14 patients developed KSHV-associated NHL. Three patients had classic KSHV-positive, Epstein–Barr virus (EBV) positive primary effusion lymphoma (PEL); five were diagnosed with KSHV positive/EBV negative visceral large B cell lymphoma with PEL-like phenotype and six developed plasmablastic lymphoma/leukaemia (3/3 KSHV positive/EBV negative) (19). This is a 15-fold increase in lymphoma risk above that seen in the HIV-infected population. The pathogenesis of these lymphomas probably differs, with the plasmablastic type driven by the expansion of plasmablastic microlymphomas seen in MCD lesions. In contrast, the PEL and PEL-like lymphomas may be driven by the cytokine-rich environment with high levels of vIL-6 and IL-10, which are known to enhance cell growth of PEL cell lines (34).

THERAPY

The diagnosis of MCD is established histologically by lymph node biopsy, which shows the typical interfollicular plasmacytosis. There are no definitive gold standard treatments for MCD. No randomized trials have been conducted because of the infrequency of the diagnosis and often only case reports have appeared in the literature. Although surgery is the mainstay of treatment for localized Castleman's disease, with complete removal of the mediastinal lesions being curative, it has a limited role in MCD. Splenectomy, in addition to establishing the histological diagnosis, may have a therapeutic benefit as a debulking procedure, as some of the haematological sequelae such as thrombocytopaenia and anaemia may in part be due to splenomegaly. Following splenectomy there is often resolution of the constitutive symptoms but this may be short lived, approximately 1–3 months, and some form of maintenance therapy is needed to prevent relapse (35).

For immunocompetent patients the chemotherapy regimes for MCD are based on lymphoma schedules such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). However, in the pre-HAART era, these schedules were associated with marked toxicity in HIV-positive patients and consequently other schedules were developed. In the largest published study from Paris of 20 patients, there was a partial response in 100% (9/9 patients) with single-agent vinblastine but only 4 patients remained stable with maintenance therapy (4–6 mg/2 weeks). Five patients relapsed and required combination chemotherapy ABV (adriamycin, bleomycin, and vincristine) regimen or partial splenectomy. Four patients received up-front ABV and only three responded with a partial response. In three patients, intermittent treatment with cyclophosphamide achieved a partial response (35). Two HIV-positive patients treated with oral etoposide for MCD led to remission of 1.5 and 6 months respectively. It should be noted that the first patient had been treated in the past with chemotherapy and ganciclovir and had multiple relapses. Treatment with 50 mg etoposide was considered safe, had minimal side effects, and was convenient to administer (36). Although there is little evidence on which to base treatment strategies, in many centre combination chemotherapy is used initially to induce remission in aggressive forms of MCD. This may be followed by gentler, single-agent chemotherapy regimens to maintain the response such as vinblastine or etoposide.

The introduction of highly active anti-retroviral therapy (HAART) has transformed HIV/AIDS in established market

economies and has been associated with a reduction in the incidence of many HIV-associated malignancies including Kaposi's sarcoma (37). Moreover, HAART has been shown to prevent the development of KS and to prolong time to treatment failure in KS (38, 39). Several small series have also demonstrated that HAART alone can be effective therapy for KS. Studies have now been undertaken to see if the addition of HAART in the treatment of MCD has any effect on morbidity and mortality. The effect of HAART has been described in seven patients with MCD and HIV infection (40). Six patients responded to chemotherapy and immune reconstitution was described in five patients. However, patients continued to require long-term chemotherapy to prevent further episodes of MCD. The mean survival was 48 months, which was longer than described in the pre-HAART era patients when most patients succumbed to opportunistic infections related to their HIV. In addition, there were no cases of plasmablastic lymphoma as a complication of MCD. Another study, by Coty et al., presented in abstract form at the 7th International Conference on Malignancy and AIDS 2003, suggested long-lasting remission in 8 of 10 HIV-positive patients with MCD after both splenectomy and HAART. However, in an early case report of three patients with AIDS treated with HAART, the development of aggressive MCD was thought to be part of the immune reconstitution disease spectrum associated with the starting of HAART (41). Unfortunately all three patients died, indicating the life-threatening nature of this disease particularly in the setting of immune reconstitution.

Specific immunotherapy has also been used as treatment for MCD. Interferon alpha (IFN α) has been administered either alone or in combination with HAART or chemotherapy for patients with MCD both to induce remission and as maintenance therapy (35, 42, 43). This cytokine is thought to have an anti-proliferative effect by directly binding to cell surface receptors and an antiviral effect by inhibiting viral replication. It also enhances the immune response by increasing natural killer cell activity and upregulating the major histocompatibility class I expression of cells infected with KSHV. In combination with vinblastine and splenectomy, it contributed to the long-term remission of 2/3 patients (35). In a recent case report a patient was initially treated with anti-viral therapy and splenectomy followed by chemotherapy to induce remission; although this was achieved chemotherapy failed to achieve sustained remission and interferon α therapy was started (43). This has led to remission for over a year. A further case report of treatment of MCD with HAART and low-dose interferon α alone has shown a sustained remission of 24 months (44). Interferon α maybe used as an alternative to chemotherapy for maintenance to produce sustained remissions of MCD with its relatively favourable side effect profile.

Since the pathogenesis of MCD is related to KSHV virus and its viral oncogenes, particularly vIL-6, monoclonal anti-IL-6 therapy has also been used in the treatment of MCD. Transgenic mice carrying human IL-6 cDNA fused with a murine major histocompatibility class-I promoter develop symptoms that resemble MCD and treatment with anti-IL-6R mAb completely prevented these and prolonged their survival (45). Seven patients were treated with atlizumab, a humanized monoclonal anti-IL-6 receptor antibody in patients with either multicentric plasma cell or mixed variant Castleman's disease. They had resolution of their immediate symptoms and by 3 months they had reduction in lymphadenopathy and hypergammaglobulinaemia with improvement of their renal function, which had deteriorated due to secondary amyloidosis. This remission was not sustained and recurrence was observed (46). Recent case reports of treatment with thalidomide also showed resolution of systemic manifestations of MCD (47, 48). Thalidomide is known to have a powerful anti-cytokine effect and inhibits tumour necrosis factor and other pro-inflammatory cytokines.

Another monoclonal antibody that has been tried is the anti-CD20 monoclonal antibody rituximab. This has been found to increase response and survival in conjunction with chemotherapy in CD20-positive lymphoma (49), possibly due to its action on IL-10 (50). Following the publication of a few case reports (51–53), a small study of five HIV-infected patients with MCD treatment with rituximab was published that reported complete remission in 60% of cases with a follow up of 2–14 months (54). Remission was accompanied by a corresponding fall in KSHV viral load and C-reactive protein. Interestingly two of these patients had an exacerbation of their KS despite no alterations in their baseline levels of viral load or CD4 counts. In keeping with the reduction in KSHV viral load with rituximab, Newsom-Davis et al. found a fall in IL-6 and TNF with resolution of their symptoms (53). It is difficult to say whether this was related to the mechanism of action of rituximab or just a reflection of the reduction in KSHV due to apoptosis of B cells.

Since MCD has been shown to be a viral-driven disease with the presence of viral genes such as vIL-6 having an effect on pathogenesis, the effect of anti-herpesvirus therapy to reduce the KSHV viral load and alleviate disease has been examined in KSHV-associated diseases in the HIV setting. In HIV-positive patients Kaposi's sarcoma incidence was reduced when prophylactic ganciclovir or foscarnet was used to prevent CMV retinitis (55, 56). Furthermore, antiviral treatment, which has led to a clinical improvement, has been shown to reduce KSHV viral load in patients with KS (57), PEL, and haemophagocytic syndrome (58). In a series of three patients treated with ganciclovir, there was a reduction in the frequency of acute symptoms of MCD for two patients treated with oral and

intravenous ganciclovir (59). For the third patient, who was on the intensive care unit, there was resolution of pulmonary and renal failure with intravenous ganciclovir. All the patients had a reduction in KSHV viral load with the ganciclovir therapy, accompanying the resolution of their symptoms. However, the use of foscarnet and cidofovir antiviral therapy was ineffective in an HIV-negative MCD patient with proven KSHV viraemia and treatment with corticosteriods in combination with chlorambucil chemotherapy was required to achieve a clinical response (60). Furthermore the KSHV viral load rose in this patient with the commencement of anti-herpesvirus therapy; this may denote that the antiviral therapy was ineffective in this case, or that once the MCD is established KSHV has a less prominent role and antiviral therapy is less effective than immunotherapy or chemotherapy.

CONCLUSION

MCD is a rare disease characterized by polyclonal lymphoproliferation. It has an increase incidence in HIV-positive patients due to the increased incidence of KSHV infection in this population. KSHV is involved in the development of this disease and recent research has shown that viral IL-6 expressed by the KSHV genome is important in the pathophysiology of MCD. The introduction of HAART for the treatment of HIV has led to a reduction in the incidence of other associated virally driven diseases including NHL and Kaposi's sarcoma. Moreover, HAART alone is often a successful treatment for HIV-associated Kaposi's sarcoma. Due to the low incidence of MCD, it is difficult to determine whether HAART has had an impact on the relative risk of MCD in HIV-positive individuals. Despite the use of HAART, other antiviral therapies, and immunological therapies to maintain remission, MCD remains a disease with a very poor prognosis in the HIV setting. The further understanding of the disease processes involved and the development of a consensus on the optimum therapeutic options remains the challenge in tackling this disease in the third millennium.

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