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MULTICENTRIC CASTLEMAN'S DISEASE: A PEER REVIEW

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ABSTRACT

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 (HIV) infection. Castleman's disease is a rare lymphoproliferative disorder in there has been recent p rogress in elucidating underlying mechanisms with potential therapeutic implications. Unicentric Castleman's disease is an indolent condition that is often treated with local approaches. In contrast, patients with multicentric Castleman's disease (MCD) have a less favorable prognosis and require systemic treatment. Cytotoxic chemotherapy, with its atten- dant risk for toxicity,has been widely used to treat MCD, with variable efficacy. The discovery of putative etiologic factors and targets in MCD, particularly human herpesvirus 8, CD20, and interleukin (IL)-6, has been translated into the use of rituximab and anti–IL-6- based therapy,,as well as antiviral agents.

KEYWORDS: Castleman, multicentric Castleman's disease, (HIV)infection.

INTRODUCTION

Castleman disease, also known as angio follicular lymph node hyperplasia, is an uncommon lympho proliferative disorder originally described in a case published in 1954.[1] The patient

from that case was a man aged 42 years who presented with high fevers, sweats, fatigue, and a non productive cough. He was found to have an anterior mediastinal mass with anemia and an elevated sedimentation rate. The treating physician suspected tuberculosis and empirical streptomycin was administered prior to complete surgical resection. The discussants favored a diagnosis of teratoma or dermoid cyst, also considering mediastinal tuberculoma, thymoma, and Hodgkin disease. Castleman presented the surgical pathology and described a new syndrome characterized by hyperplasia of mediastinal lymph nodes with regressed germinal centers. The disease did not recur in this patient following surgical resection. This case, followed 2 years later by a case series described what is now known as unicentric Castleman disease (UCD), which is distinct from multicentric Castleman disease (MCD), a condition with unique clinical and pathological features.

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 it is 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 inter follicular 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.

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 [2]. 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 [3-4]. 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 plasma cytosis similar to that found in MCD, as well as accelerating haemopoesis and inducing vascular endothelial growth factor (VEGF), a pro- angiogenic cytokine.[5] 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.[6] 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.[7] It is intriguing that PEL cell lines are dependent on vIL6 but not hIL6, despite the lackof 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.[8] 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,[9] 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 plasma- blastic 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 lym- phoid tissue and in 6 out of 8 microlymphomas. In two cases of the microlymphomas and two plasma- blastic lymphomas, the KSHV-positive plasmablasts were monoclonal.[10]

Multicentric Castleman Disease Epidemiology

MCD commonly presents in the sixth decade of life, although patients with HIV infection tend to present at a younger age.[11,12,13] A slight male predominance is seen in MCD. HIV infection is an important risk factor for MCD, and all patients with HIV-associated MCD are co infected with HHV-8. HHV-8 infection is present in approximately 50% of HIV-negative cases of MCD and varies with the HHV-8 seroprevalence of the population. Large population studies have revealed an in- creased incidence of HIV-associated MCD since the introduction

of antiretroviral therapy, which is in contrast to the marked decline in incidence of HIV-associated Kaposi sarcoma.[14] The mechanism of this increase is unclear, but such an increase may reflect improved survival rates, longstanding immune dysregulation associated with long-term HIV infection, or an increased awareness of the disease among health care professionals.

Clinical Presentation

Systemic inflammatory manifestations characterize the vast majority of patients with MCD who present with fevers, night sweats, weight loss, and fatigue. Physical examination is typically notable for general- ized lymphadenopathy and hepatosplenomegaly, and many patients have evidence of fluid retention with lower extremity edema, pleural and pericardial effu-sions, and abdominal ascites. Common hematological abnormalities include anemia, elevated inflammatory markers, hyper gamma globulinemia, and hypoalbuminemia. Systemic symptoms and hematological abnormalities have been shown to correspond to elevated inflammatory markers and cytokine levels, particularly IL-6 and IL-10. The natural history of MCD is variable. Some patients may present with indolent disease and very slow progression over months to years, while others will experience a relapsing-remitting course or an acute and fulminant disease that can be fatal within weeks; the latter courses are more common in pa- tients with HIV-associated MCD.[15,16] HIV-associated MCD may also concurrently or sequentially present with other concomitant malignancies, including Kaposi sarcoma or primary effusion lymphoma, each of which share an HHV-8–mediated pathogenesis. Kaposi sarcoma may be identified in 72% of HIV-related MCD cases at diagnosis and may be seen in HIV-negative MCD, although at a far lower rate. Patients are also at significant risk for diffuse large B-cell lymphoma, which may arise directly out of HHV-8–positive MCD; therefore, one must consider the possibility of a second malignancy at the time of diagnosis and perform a thorough skin exam- ination for cutaneous Kaposi sarcoma, as well as consider biopsying bulky or visceral locations seen on imaging studies for staging that may constitute a distinct histology from Castleman disease. Repeat biopsy should also be considered at progression or relapse to evaluate for lymphomatous transformation. Patients with HIV-associated MCD will often present with a low CD4 count, so concomitant opportunistic infections must also be considered at diagnosis and during the course of illness, including Pneumocystis jiroveci, Toxoplasma gondii, cytomegalovirus, and mycobacterial infections, among others.

CURRENT THERAPEUTIC OPTIONS

In UCD patients,complete surgical excision of the affected lymph node affords a high cure rate.[17,18] Radiotherapy could be a valuable alternative when complete resection of disease is technically difficult,[19] The management of MCD patients is more complicated and their prognosis is less favorable. Several therapeutic options have been employed in MCD patients with variable activity, although there is still no consensus regarding the gold standard therapeutic approach.[20] With a better understanding of the underlying biology of MCD, new approaches are under development.

Cytotoxic Chemotherapy

Most reports regarding the activity of antineoplastic agents in MCD patients are drawn from a few anecdotal cases and small case series. These data should be interpreted cautiously in the context of the nonuniformity of the response criteria, the infrequency of the disease, and the heterogeneity of the patient population. In addition to the lack of randomized comparative trials, the scanty information available regarding duration of response and side effects of therapy confound interpreting he benefit of such treatment. Various single-agent cytotoxic drugs have been used to treat MCD patients, including chlorambucil, corticosteroids, cyclophosphamide, 2chlorodeoxyadenosine, carmustine, vincristine, and bleomycin. Single-agent liposomal doxorubicin, oral etoposide, and vinblastine were reported to produce durable remission, predominantly in HIV patients .[21,22,23] Particular attention should bepaid to this vulnerable population because of the risk for infection and the potential life-threatening interaction between antiretroviral therapy and antineoplastic drugs.[24]

Immunomodulators

Interferon Significant clinical benefits have been described from singleagent interferonfor treating patients with Castleman's disease. It was used initially in HIV patients, but later was found to be beneficial for HIVpatients.One case complicated by pancytopenia required treatment interruption,[25] even though interferon was well tolerated in most cases .Interestingly, interferon-was successful in yielding long-term complete remission in patients off treatment for as long as 4 years,[26] The precise underlying mechanisms of the sesalutary out comes haven fully characterized but could be a result of several diverse biologic effects of interferon, including inhibition of transsignaling via Down regulation of IL -6R, antiviral effects such as inhibition of HHV-8 replication, and up regulation of human leukocyte antigenclass1expressionon HHV-8–infected cells leading to cell-mediated destruction.[27,28]

Corticosteroids

Variable benefit has been achieved with the use of corticosteroid agents. They are rarely chemotherapybecause steroid-induced remissionis usually short lived.[29,30] Assessing their benefitin MCD patients has been hampered by their use in combination with cytotoxic drugs. Moreover, the lack of information regarding the usual side effects of steroids, such as a higher risk for infection, osteoporosis, and metabolic abnormalities, make it difficult to estimate their impact in managing the disease.

Thalidomide

Thalidomide is part of the therapeutic arsenal in plasma cell malignancies, particularly multiple myeloma, wherein IL-6 plays a central role in disease activity [31]. Several encouraging reports indicate a beneficial effect of thalidomide in patients with MCD . Thalid- omide was shown to selectively downregulate the ex- pression of IL-6 and tumor necrosis factor in peripheral blood monocyte cells from healthy volunteers.[32] Its therapeutic value in CD patients might therefore result fromdisruptingIL-6production.InapatientwithCDas- sociated with pemphigus vulgaris, the IL-6 level de- creased significantly concordantly with clinical improvement [33]. Other reports demonstrated a decline in the level of CRP, a surrogate of IL-6 activity.[34]

Anti-Interleukin 6 Therapy

Siltuximab and tocilizumab are monoclonal antibodies targeting IL-6 and its receptor (IL-6R), respectively. The US Food and Drug Administration (FDA) has approved siltuximab for the treatment of patients with HIV negative, HHV-8 negative MCD, where it shows significant clinical activity, resulting in control of IL-6–dependent systemic symptoms and laboratory abnormalities.[35,36] A phase 2 study that included 19 patients with HIV negative and HHV-8 negative MCD reported 8 radiological re- sponses, including 1 complete response. At a me- dian follow-up of 5.1 years (range, 3.4–7.2 years), all 19 patients taking siltuximab therapy were still alive. The data from those studies prompted a multi- center, randomized, double-blind, placebo-controlled trial of siltuximab in patients with HIV negative features make these patients appealing candidates for therapies targeting IL-6. Although vIL-6 is implicated in the pathogenesis of HHV-8-associated MCD and is not targeted by the current monoclonal anti- bodies, human IL-6 is also elevated in the majority of patients with HIV-associated MCD and likely re- mains a significant contributor to disease activity and symptomatology.12 Three cases in the literature have demonstrated activity of

IL-6 targeted therapy in HIV and HHV-8-associated MCD,[37,38] speaking to the need for prospective clinical trials in these patients.

CONCLUSION

Castleman disease is an uncommon lymphoproliferative disorder that continues to pose clinical challenges. Although surgical resection remains the standard therapy for unicentric disease, the landscape for the management of multicentric disease continues to evolve. Rituximab monotherapy is the current mainstay of therapy, and novel agents targeting interleukin 6 represent exciting new additions to the treatment armamentarium. Single-agent and combination chemotherapies as well as antiviral therapy provide adjunctive support, particularly in the setting of relapsed or refractory disease Currently, good results have been realized through targeting HHV-8replication,CD20, andIL-6path- ways. The anti–IL-6R antibody tocilizumab is an effective treatment tha thas been approved in Japan for CD treatment. Siltuximab, an anti–IL-6 antibody, is also highly effective and is currently in prospective trials in the U.S. and elsewhere [39,40].Sideeffects are few to none. Rituximab has produced durable responses.

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