Castleman's Disease - Clinical, Histological and Therapeutic Features

RADU DRAGOS MARCU[1,2], ARSENIE DAN SPINU[1,2]*, BOGDAN SOCEA[3,4], MARIA OANA BODEAN[5], CAMELIA CRISTINA DIACONU[6,7], FLORINA VASILESCU[8], TIBERIU PAUL NEAGU[9,10], OVIDIU GABRIEL BRATU[1,2]

[1]Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 3, 37 Dionisie Lupu Str., 020021, Bucharest, Romania

[2]Dr. Carol Davila Central Military Emergency University Hospital, Bucharest, Department of Urology, 88 Mircea Vulcanescu Str., 010825, Bucharest, Romania

[3]Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 10, 37 Dionisie Lupu Str., 020021, Bucharest, Romania

[4]Saint Pantelimon Clinical Emergency Hospital, Bucharest, Department of Surgery, 340-342 Pantelimon Road, 021659, Bucharest, Romania

[5]Emergency University Hospital Bucharest, Department of Obstetrics and Gynecology, 169 Splaiul Independentei, 050098, Bucharest, Romania

[6]Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 5, 37 Dionisie Lupu Str., 020021, Bucharest, Romania

[7]Emergency Clinical Hospital Bucharest, Department of Internal Medicine, Bucharest, 8 Calea Floreasca, 014461, Bucharest, Romania

[8] Dr. Carol Davila Central Military Emergency University Hospital, Bucharest, Department of Pathology, 134 Calea Plevnei, 010825, Bucharest, Romania

[9]Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 11, 37 Dionisie Lupu Str., 020021, Bucharest, Romania

[10]Emergency Clinical Hospital Bucharest, Department of Plastic Surgery and Reconstructive Microsurgery, 8 Calea Floreasca, 014461, Bucharest, Romania

Castleman's disease (CD) is a rare and benign lymphoproliferative pathology, characterized by lymphoid tissue hyperplasia, process that can occur at any site of the lymphoid chain. The purpose of this paper is to review the existing data regarding Castleman's disease etiopathogenesis and treatment. Considering the extent of the lymphoid tissue involvement Castleman's disease can be classified as unicentric (UCD) and multicentric (MCD). Another classification of this pathology is based on the histopathological features: hyaline vascular CD (90% of cases), plasma cell CD (less than 10%) and mixed cell type. Patients with UCD have good prognosis, the gold standard treatment being complete surgical excision. The multicentric type in contrast to UCD has a worse prognosis and associates the risk of evolving to lymphoma. Over the years different therapeutic strategies have been applied in the management of multicentric Castleman's disease: glucocorticoids, chemotherapy, antiviral agents and monoclonal antibodies that target CD (cluster of differentiation) 20, interleukin -6 (IL-6) and IL-6 receptors. Castleman's disease is a rare and complex pathology, whose etiopathogenesis is still incompletely elucidated. In the past few years the overall survival and progression free survival has significantly increased, due to different therapeutic options that have emerged, options that have constantly offered better and better results. Further investigation regarding the chemical interactions between different receptors and therapeutic molecules, understanding the mechanism of action and the potential benefits of each therapeutic agent may prove useful in clinical practice for treating CD.

Keywords: Castleman's disease, etiopathogeny, clinical features, treatment, outcome.

Castleman's disease (CD) is a rare and benign lymphoproliferative pathology, characterized by lymphoid tissue hyperplasia, process that can occur at any site of the lymphoid chain. This pathology was first described by *Benjamin Castleman* in the mid-1950s and it is also known as angiofollicular lymph node hyperplasia or as giant lymph node hyperplasia [1,2]. Even though it has been more than 50 years since it was first described, official definition of the disease and the ICD (*International Statistical Classification of Disease and Related Health Problems*) code (*ICD-10-CM D47.Z2*) were published in October 2016. Therefore, the true incidence of this disease is yet to be discovered, at the moment, two major databases reported rates of 21 and 25 per million person-years [3].

The most common site of Castleman's disease is the mediastinum, accounting for over 60% of cases, followed by the cervical region (neck and head lymph nodes) and rare cases that involve the pelvic area, the axillary and retroperitoneal space [4-6].

Considering the extent of the lymphoid tissue involvement, Castleman's disease can be classified as unicentric (single site lymphoid hyperplasia) and multicentric (widespread lymphoid tissue proliferation). Another classification of this pathology is based on the histopathological features: hyaline vascular CD (90% of cases), plasma cell CD (less than 10%) and mixed cell type [7,8].

Up to 90% of cases with UCD associates the hyaline vascular type and appears more frequently in young patients, in the third and fourth decade of life, while the plasma cell type is characteristic for MCD and appears in older patients, usually in the sixth life decade [9-11]. There are other tumors that are aged related, but this one proves to be much more difficult to manage in elderly [12].

In this article, after reviewing the most recent papers regarding this pathology, we summarized the most relevant data in order to be of use to clinical practitioners.

* email: dan.spinu@yahoo.co.uk

All authors had equal contribution to this manuscript

Etiopathogenesis

The etiology and pathogenesis of UCD is unclear, while numerous studies have reported the implication of human herpes-virus 8 (HHV-8) in the pathogenesis of MCD, especially in immunodeficient patients like HIV-positive patients, but not all HHV-8 positive patients are HIV positive. Immunodeficiency permits HHV-8 to elude the immune response, replicating in the lymph nodes and releasing pro-inflammatory agents like viral IL6, human IL6 and other molecules implicated in the inflammatory process, which will lead to B-cell and plasma cell proliferation, activation of the T cells and macrophages, high levels of vascular endothelial growth factor and angiogenesis [13,14]. IL-6 interferes with different organs [15-17], especially liver functions: inflammatory protein secretion, albumin production (IL-6 reduces albumin production which is associated with a decrease of the oncotic pressure, this leading to peripheral oedema, pleural and pericardial effusions), hepcidin metabolism and iron homeostasis (high levels of IL-6 upregulates hepcidin, this resulting in higher levels of iron deposits and lower levels of serum iron that is available for hemoglobin and erythrocytes production, this leading to anaemia) [14-17].

Another form of MCD is the idiopathic type in which the patients are HHV-8 and HIV negative. The explanation behind the high level of the pro-inflammatory cytokines is unclear, despite the fact that several hypotheses have been emitted over the years: auto-inflammatory mechanism, a non-HHV-8 viral implication or ectopic neoplastic secretion of cytokines [18-21]. Autoantibodies which are characteristic for certain autoimmune pathologies (systemic lupus erythematosus, Still's disease, rheumatoid arthritis, Sjögren syndrome, and myasthenia gravis) stimulate cytokine production (IL-6 and other cytokines) via lymph node antigen-presenting cells. The histological study of the lymph nodes encountered in several autoimmune pathologies like rheumatoid arthritis and systemic lupus erythematosus has revealed identical histological features to the lymph nodes encountered in the MCD [22-25].

Clinical aspects

Regarding the clinical presentations this differs between the two types of CD, the unicentric type and multicentric CD (MCD). Depending on the dimensions of the lymphoid tumor, the patients with UCD may be asymptomatic, the discovery of the tumor being incidental when performing routine imaging examinations for other pathologies; they may also present symptoms related to nearby tumor compression, especially in large tumors. The most frequent cases of UCD are located in the mediastinum and cervical area (chest over 30%, neck and head over 20%), followed by the intra-abdominal space (up to 20%) and the retroperitoneal space, which accounts for up to 10-15% of UCD cases. Other less common sites for UCD are the pelvic area, axilla and the groin region (less than 10% of all cases) [1,3,9,11]. Therefore, depending on the location of the tumor, patients with large tumors may present chest discomfort or pain, dyspnea, cough, haemoptysis, abdominal or back pain, discomfort, urinary obstruction due to ureteral compression which may lead to a renal colic, bowel compression, sub-occlusive intestinal syndrome or icterus [9,26,27]. Patients with UCD have good prognosis, the gold standard treatment being complete surgical excision, which has proven over the years to be the curative treatment for this pathology as it is for other type of tumors [28-30]. For patients with well-vascularized large tumors, preoperative angiography with selective embolization should be performed in order to reduce the bleeding risk. Radiotherapy is a viable alternative for the patients for whom the operative risks are too high or for whom a complete surgical excision is not possible, often this type of treatment providing good results [31-37]. Several studies have reported good results of neoadjuvant treatment in patients with large tumors – UCD, tumors that involved vessels like the vena cava, aorta, and iliac vessels. The neoadjuvant radiotherapy or rituximab has resulted in tumor downsizing, which further permitted surgical excision [34,38].

The retroperitoneal location of the Castleman's disease is rare, but when it occurs, it can associate important urinary symptoms due to nearby urinary tract compression. These patients may present urinary retention, ureterohydronephrosis, dorsal lumbar pain, renal colic, haematuria, recurrent urinary tract infections. Persistent or neglected ureterohydronephrosis can lead to renal function impairment with acute or chronic renal failure, renal parenchyma atrophy pyonephrosis, renal or retroperitoneal abscess formation and urosepsis [39]. The management of such complications may require hemodialysis, urinary drainage (ureteral double JJ stent insertion or nephrostomy tube placement), ultrasound or CT guided abscess drainage or nephrectomy [40-45].

MCD is characterized by high levels of inflammatory markers and cytokines (especially IL-6) which lead to systemic symptoms, also known as B-symptoms. Therefore, patients with MCD may present fever, chills, night sweats, loss of appetite, weight loss, fatigue, therefore, a plethora of symptoms [46,47]. Physical examination could reveal generalized lymphadenopathy, hepato-splenomegaly, vascular leak syndrome (ascites, peripheral oedema, and pleural and/or pericardial effusions), and skin lesions. Laboratory tests may present anaemia, thrombo-cytopenia, high levels of CRP, IL-6 and VEGF, hypo-albuminemia, hypergammaglobulinemia. Patients with MCD may associate POEMS syndrome (polyneuro-pathy, organomegaly, endocrinopathy, M-protein, skin pigmentation), amyloidosis, IG4- related disease, TARFO syndrome (thrombocytopenia, anasarca, fever, reticulin myelofibrosis, organomegaly), Kaposi sarcoma, Hodgkin or non-Hodgkin lymphoma [2,9,48]. The multicentric type in contrast to UCD has a worse prognosis and associates the risk of evolving to lymphoma. According to literature MCD presents a rate of mortality that can be as high as 40% during the first ten years after the diagnosis was made [49].

Histological features

The hyaline vascular type is characterized by vascular proliferation and hyalinization of the vascular walls. When other comorbidities are associated, calcification inside the vessel wall may be seen [44,50]. Compared to normal lymph node follicles the hyaline vascular type lymph follicles present a series of changes: the mantle zone is enlarged by numerous small lymphocytes arranged in concentric rings (similar to the onion layers) around the germinal center which is atrophic and radially penetrated by hyalinised vessels (lollipop follicles). The lymph follicles show regression features due to the fact that an increased number of dysplastic follicular dendritic cells can be seen in the germinal centers, particularity that may also lead to malignant pathologies such as dendritic cell sarcoma [9,10,51,52]. Mantle zones from different, adjacent follicles may fuse and lead to the appearance of a large follicle with two germinal centers - the *twining* phenomenon. The interfollicular areas are characterized by vascular

proliferation with hyalinization of the vessels walls. Microscopic examination may also reveal obliterated medullar sinuses. A small percentage of plasma cells can be found in the interfollicular areas. The cases where this percentage is higher than usual suggests the mixed type of Castleman's disease. This subtype implies the presence of both hyaline vascular type and plasma cell variant elements (fig. 1) [9,10,52].

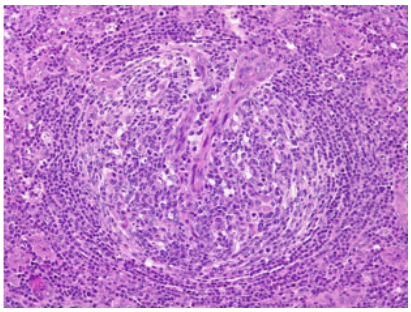

Fig. 1: Castleman's disease – hyaline vascular type – lymphoid follicle crossed by a epithelioid venula (HE staining, x20)

The plasma cell type is characterized by lymph nodes with preserved architecture, with normal size or enlarged follicles with hyperplastic germinal centers and normal follicular dendritic cells. The interfollicular areas are characterized by sheets of plasma cells and mild vascular proliferation with or without hyalinization of the vessel walls, the latter being more frequently encountered in the mixed variant (fig. 2). Most often, the plasma cells are polytypic, but they may also present monotypic immunoglobulin's G or A, especially lambda light chains (fig. 3-6) [9,52,53]. These histological features can also be encountered in other reactive, inflammatory and malignant pathologies, that are accompanied by lymph node hyperplasia: infections, HIV, EBV and IgG 4 related lymphadenopathy, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, amyloidosis, sarcoidosis, Sjogren syndrome), B cell lymphoma, plasmacytic neoplasia, multiple myeloma, Hodgkin or non-Hodgkin lymphoma, lung giant cell carcinoma, clear cell or choroid meningioma [10,54]. Another histological CD subtype is the plasmablastic variant which is characteristic for the HHV-8 positive cases. The lymph nodes show a mixture of changes that could be encountered both in the hyaline vascular variant as well as in the plasma cell subtype, with blurring of the boundary between the germinal center and the mantle zone of the lymph follicles. In the mantle zones plasmablasts can be identified, which have been noticed to express monotypic IgM, light lambda chains, but molecular studies have shown that they are in fact polyclonal [9,10,53]. In some cases, the plasmablasts can fuse and form micronodules, which may progress, leading to pre-neoplastic changes and furthermore to large B-cell lymphoma.

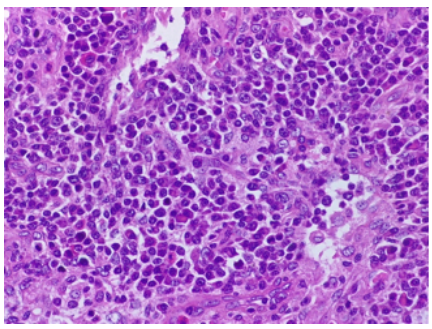

Fig. 2. Castleman's disease plasma cell type interfollicular area with lots of plasma cells (HE staining, x40)

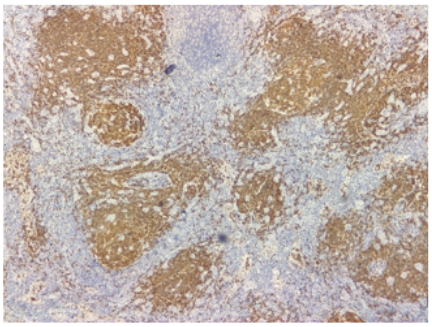

Fig. 3. Castleman's disease plasma cell variant positive for CD 20 immunohistochemistry staining (x5) in lymphoid follicles

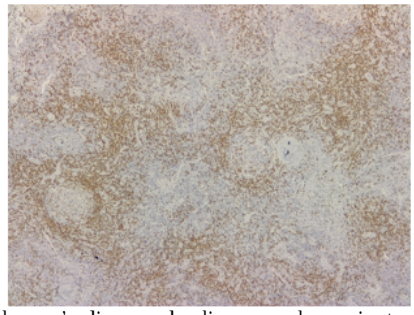

Fig. 4. Castleman's disease hyaline vascular variant positive for CD 3 immunohistochemistry staining (x5) in perifollicular lymphoid cells

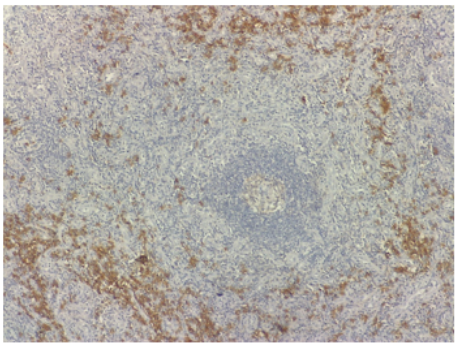

Fig. 5. Castleman's disease – positive CD 38 immunohistochemistry staining (x10) in plasmocyte cells

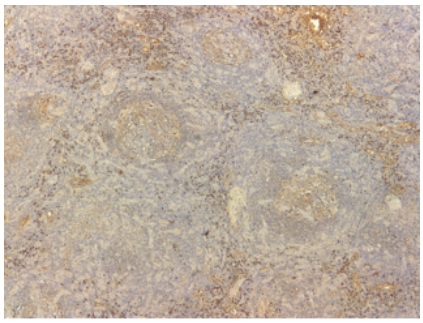

Fig. 6. Castleman's disease - positive lambda chains immunohistochemistry staining (x5) in plasmocyte cells

Fig. 7. Zidovudine chemical formula

Immunohistochemical staining may prove useful in distinguishing malignant from benign cells, in establishing differential diagnosis between different diseases that may resemble in common staining. In CD, the immunohistochemistry highlights the particularities of the lymph nodes architecture and the connections between the development of the disease and the presence of viruses, while in other pathologies, may describe the behavior of the disease [15,30,35,47]. CD 3 may be used to identify T cells in cancer or benign proliferation, CD 20 may be used to identify B cells, while CD38 is present in plasma cells. A

limited expression of kappa or lambda chains may express monoclonality and a proliferation process.

Treatment management

Several studies have reported excellent results after complete surgical excision of UCD, the patients presenting high survival rates of over 90% and very low rates of recurrences [6,55,56]. *Li Yu* reported that out of 33 patients for whom total surgical resection was performed, complete remission was obtained in 30 cases, 3 patients needing further surgery [57]. After a median follow-up period of 50 months in a recent study on 14 patients, no signs of recurrence were present [14]. For the patients who present symptoms secondary to adjacent organ compression, but for whom complete surgical resection is not possible due to high intraoperatory vascular risks, radiotherapy or debulking surgery fallowed by radiotherapy can be viable solutions. Regarding the efficiency of radiotherapy, a recent review reported that out of 17 patients who have been treated using this approach 35% achieved complete response and 41% obtained partial response [6]. *Li Yu* reported good results using radiotherapy and systemic therapy with rituximab, as an alternative for the patients for whom surgery was not possible at first, obtaining a decrease of the tumor mass with more than 50% in two patients, which then permitted complete surgical resection and complete remission in another case after radiotherapy with 4500 cGY fractioned in 30 sessions [57]. Intensity-modulated radiotherapy has shown lower toxicity due to a reduced dose of radiations that is administered to the adjacent normal structures, therefore it should be preferred to conformal three-dimensional radiotherapy [11]. Systemic options should be considered for the patients for whom surgery and radiotherapy are contraindicated or for the patients for whom these therapeutic options have failed.

Over the years different therapy strategies have been applied in the management of *multicentric Castleman's disease:* glucocorticoids, chemotherapy, antiviral agents and monoclonal antibodies that target CD 20, IL-6 and IL-6 receptor.

Glucocorticoids have proven to be efficient in the management of the acute B-symptom phase, but on the long term their efficiency is limited, with a complete remission rate that it is estimated to be less than 15 %, the patients being predisposed to recurrence within 12 to 24 months if they are treated only with glucocorticoids [9,18,57]. *Kawabata* reported that two patients out 18 who have been treated only with prednisolone have achieved complete remission of MCD symptoms and he also mentioned that these patients could develop secondary diabetes [48]. It is also known that this therapy may cause secondary osteoporosis and may interfere with the normal bone remodeling and healing process [58,59]. Several studies have reported an efficacy rate of over 80% regarding the control of the acute phase symptoms, especially in patients that may associate renal impairment [60] and considering the delayed response of rituximab it has also been suggested that glucocorticoids should be used in association with rituximab [9,55,61].

In the mid-1990s, after the introduction of *antiretroviral therapy* (ART), a significant decrease in HIV and HHV-8 positive MCD patients' mortality has been seen, with an overall survival rate increased from 14 months before introducing combined ART to approximately 80% over a period of 24 months after ART [61-66]. In 2004 *Casper* noted good results on ganciclovir treatment in three patients with HIV and HHV-8 positive MCD [67]. A pilot study conducted on 14 patients with HIV and HHV-8 associated MCD, who have received high doses of zidovudine (fig. 7) and valganciclovir (fig. 8), reported that 12 patients have achieved an important clinical improvement, as well as in terms of laboratory findings, in half of the cases. The authors also reported that the average progression free survival was six months, further therapy being needed in some cases [66]. In contrast to the results that have been presented by the previous study, *Hoffmann* has encountered low results of antiretroviral therapy in HIV associated MCD. It was noticed that only 3 patients out of the total 12 who have received antiretroviral therapy alone or in combination with chemotherapy have achieved prolonged remission [64].

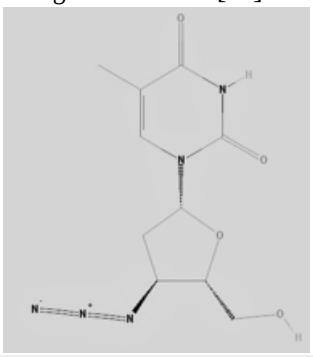

Fig. 7. Zidovudine chemical formula

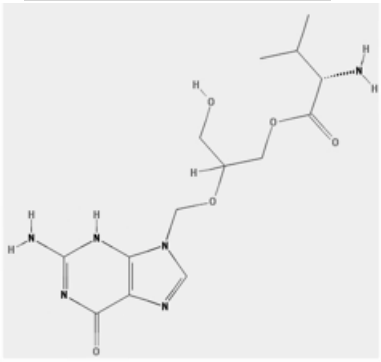

Fig. 8. Valganciclovir chemical formula

Over the years *chemotherapeutic* agents have been used in the management of MCD, either as single agents (oral etoposide, cyclophosphamide, vinblastine, cladribine, chlorambucil, doxorubicin) or in combination with other chemotherapeutic agents (CHOP: cyclophosphamide/ doxorubicin/ vincristine/ prednisone; CVP: cyclophosphamide/ vincristine/ prednisone; CVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone) or with other drugs (rituximab, steroids), usually the doses and the administration schedule being similar to lymphoma. Oral 50 or 100 mg of etoposide administered daily for two weeks or intermittent 100 mg/m^2 administered intravenously once a week for one month has proven to alleviate the symptoms and to control the disease, but these results are short lived, a high percentage of the patients presenting recurrence and disease progression after the treatment was stopped [9,10,68]. Similar results have been obtained with 4 to 6 mg/m2 of vincristine administered every two weeks until the symptoms are controlled, but in order to prevent recurrence it is recommended a maintenance program, monitoring toxicity and possible adverse reactions that could appear during the treatment [9,68]. Cladribine is another chemotherapeutic agent that has proven to be efficient in the management of MCD, but the existing trials are limited, being based on very small lots of patients. *Colleoni* achieved complete remission with cladribine, which lasted for more than two years, but both patients that were treated using this agent developed non-Hodgkin lymphoma [69]. *Chan*

reported that out of 22 patients treated with combinations of chemotherapeutic agents (CHOP, CVAD) eight patients achieved complete remission, the median follow-up period ranging between 8 and 119 months [9]. It should be noted that the patients who are managed with cytotoxic chemotherapy have high risks of developing severe side effects and infections [70-72].

Rituximab is a monoclonal antibody that targets CD20 expressing cells. Several studies have analyzed its efficiency and have concluded that this agent is a viable solution in the management of MCD, especially in HIV and HHV-8 positive MCD patients. The majority of the HHV-8 infected cells are located in the mantle zone and present plasmacytic differentiation. They may also present CD20 on their surface, but the percentage of CD20 expressing plasmablasts is small. Therefore, it is speculated that the effect of rituximab is in fact secondary to its action against the CD20 HHV-8 infected B cells that are located in the mantle zone and less to its direct action against the plasmablasts [64,73]. According to a recent study, complete symptoms remission was found in 95% of the cases and 79% of the patients did not present any signs of recurrence after a period of follow-up of 24 months [74]. In another article, published in 2011, *Bower* reported the results of a retrospective study based on 49 HIV positive MCD patients treated with rituximab alone or in combination with chemotherapy (etoposide), the latter being used for the patients who presented poor performance status. The overall survival rate at five years was 90 and 61% of the patients did not present recurrences [64]. *Uldrick et al.* reported that after only two cycles of rituximab and doxorubicin 88% of the patients with MCD presented complete symptoms response and at the end of the treatment the rate was 94%. In terms of biochemical response 88% of the patients achieved significant improvements. The overall survival rate after 36 months was 81% and the progression free survival rate was 69% [73]. Special attention should be given to the HIV positive CMD patients during treatment with rituximab due to the risk of Kaposi sarcoma flare-ups, this being the most common adverse event that could occur, with an incidence that it is estimated to range between 35 and 67% [9,73,74].

HIV positive MCD patients present a high risk of developing non-Hodgkin lymphoma, being estimated to be 15-fold higher than that encountered in HIV positive patients, but without Castleman's disease. *Gerard* conducted a study on 113 HIV positive MCD patients regarding the capability of rituximab therapy in reducing the risk of evolution towards non-Hodgkin lymphoma and concluded that the rituximab lot presented a much lower risk of developing non-Hodgkin lymphoma when compared with the group without rituximab, with an 11-fold lower [63].

The first report of *Interleukin-6 targeting (IL-6) therapy* in MCD dates back to 1994, when Beck presented the case of a patient with MCD who was treated with a monoclonal antibody that targeted IL-6 (BE-8). Soon after initiating the treatment, significant improvements in terms of disease symptoms and laboratory findings have been seen [75].

Siltuximab is a humanized monoclonal antibody that targets IL-6 and prevents it to bind with the IL-6 receptor. This agent has offered excellent results in HIV and HHV-8 negative MCD patients in terms of efficacy, disease control, overall survival and patient tolerability regarding its toxicity. Based on the results of a randomized double-blind placebo controlled clinical trial that was published in 2014, siltuximab was approved as a valid therapeutic option in the management of HIV and HHV-8 negative MCD patients by US FDA (*Food and Drug Administration*) and European Medicines Agency [76].

In 2013, *Kurzrock* published the results of a phase I study regarding the outcomes of siltuximab therapy in patients with B-cell non-Hodgkin lymphoma, multiple myeloma and Castleman's disease [77]. 37 patients with Castleman's disease (35 with MCD and two patients with inoperable UCD) received escalated doses of siltuximab of which 19 patients achieved important clinical benefit (1- complete remission, 11- partial remission, 7- stable disease. In terms of adverse events, the most common were: thrombocytopenia (25%), neutropenia (19%), leukopenia (18%), anaemia (10%), hypertriglyceridemia (19%) and hypercholesterolemia (15%). There was no dietary recommendation in order to reduce the progression of disease, as seen in other pathologies [78,79]. No dose cumulative toxicity has been noted during the trial [14,77]. These 19 patients that responded to the siltuximab treatment have been included in an extended phase II study in order to evaluate the long-term safety and efficiency of siltuximab therapy. 14 patients were treated for approximately 4 years and the overall survival rate at 5 years was 100%. Adverse events such as upper respiratory infections (90%), nausea (63%), vomiting (58%), extremity pain, headaches, rash and increased levels of triglycerides (each over 40%) have been reported since the start of the rituximab treatment. During the phase II trial the patients presented usually the same adverse reactions, but the rate of complications was smaller [14,76].

In 2014, van *Rhee* reported the outcomes of the first randomized double blinded placebo controlled clinical study concerning the outcomes of siltuximab in MCD patients (KSN14-7). Out of 79 HIV and HHV-8 negative MCD patients 53 have received siltuximab and in 26 cases placebo was administered. The primary end point consisted in durable symptoms and lymph node response for more than 18 weeks and it was achieved in 34% of cases where siltuximab was the drug of choice, in contrast to the placebo group where none of the patients have achieved the goals that have been established at the beginning of the study. Siltuximab also provided significant improvement in terms of anaemia, inflammatory markers and hypoalbuminemia [80].

Another agent that interferes with IL-6 activity is tocilizumab, which is a humanized 1k immunoglobulin monoclonal antibody that binds with the IL-6 receptor and blocks the IL-6 induced inflammatory pathway [10,48]. In 2005, a Phase II, open label, single armed study conducted on 28 MCD patients (26 patients with idiopathic CD and two patients with HIV negative but HHV-8 MCD) who have received 8mg/kg of tocilizumab every two weeks over a period of four months has demonstrated that this drug can offer significant disease control and it can also improve the patient's quality of life. This treatment was associated with important symptom control, improvement of the inflammatory markers, 64% of the patients presenting significant decrease of the CRP levels and 71% of the fibrinogen, as well as with anaemia, albumin level and lymph nodes (more than half of the patients presenting lymph node size reduction). Upper respiratory tract infections were the most frequent adverse events, being encountered in approximately 57% of the cases, followed by malaise (21%), pruritus (21%), and diarrhea (18%) [81]. Based on these encouraging results, tocilizumab was approved in Japan, while in US it is approved for rheumatoid arthritis and juvenile idiopathic arthritis, despite the fact that other small studies present similar positive results [14,17,81].

Reports regarding the efficiency of tocilizumab in HIV and HHV-8 positive MCD patients are limited, but two studies have presented short term good outcomes in such patients after the use of tocilizumab [82].

There are patients for whom IL-6 targeting therapies do not provide a significant improvement, this suggesting that there may be other proinflammatory cytokines that could have an important role in MCD pathogenesis [57]. Anakira is an IL-1 receptor antagonist and it is supposed to be effective in the MCD treatment by interfering with the IL-1 signaling pathway and by blocking IL-6 production [10]. Several small studies have reported good results after treatment with anakira [83].

Turcotte presented in 2014 the first case report regarding the efficiency of tocilizumab in pediatric patients with MCD. After initially treating the patient with rituximab and methylprednisolone, but without any signs of improvement, the treatment was switched to tocilizumab and anakira. The patient's status significantly improved and he was discharged six weeks later after receiving two doses of tocilizumab and anakira for two weeks. The patients continued with chemotherapy – CHOP and tocilizumab, anakira being discontinued. 7 months after completing the tocilizumab treatment and 13 months after chemotherapy no signs of recurrence were found [84].

It has very well been established the efficiency of rituximab in the management of HIV positive patients in contrast to HIV negative MCD patients where unfortunately this drug did not lead to sustained disease remission, making it the first line treatment in HIV associated MCD [14]. A 2017 retrospective study evaluated the efficacy of different types of treatment in both HIV and HHV-8 positive and negative patients. The authors reported that over 50% of the HIV and HHV-8 positive MCD patients that have been treated with rituximab or rituximab-based therapies presented a response and that complete remission was achieved in 20% of these cases. In the idiopathic MCD lot of patients it was noticed that rituximab provided a lower complete remission rate and a lower progression free survival rate than siltuximab, which has offered better results in this type of patients. When compared to chemotherapy or to corticosteroids it has also been observed that the results that have been achieved with the rituximab treatment did not prove to be superior in terms of complete remission and progression free survival. The rituximab therapy provided superior progression free survival rates for HIV and HHV-8 positive patients than for the idiopathic MCD cases. The authors also reported that the non-TARFO (*Thrombocytopenia, Anasarca, Reticulin myelofibrosis, Fever and Organomegaly*) group of patients associated higher survival rate than the TARFO patients and that siltuximab therapy provided better results when compared with rituximab, chemotherapy and corticosteroids [57].

Several studies have reported good results of IL-6 targeting agents in idiopathic MCD patients. These results have led to the approval of siltuximab in 2014 as a valid therapeutic option for idiopathic MCD by FDA and by the European Medicines Agency [76]. Previous to this, after a 2005 study report, Japan approved tocilizumab for the management of idiopathic MCD [14]. For the patients who fail to respond to siltuximab or show signs of disease progression single agent chemotherapy (etoposide, vinblastine, and doxorubicin) should be considered. In selected cases rituximab can be associated to the single agent chemotherapy. If the general status does not improve and the patient is facing a new relapse episode or is refractory to the previous therapeutic scheme an alternative single agent or combined chemotherapy should be considered, siltuximab, tocilizumab or bortezomib.

For the HIV positive MCD patients who fail to respond to the rituximab approach, single agent chemotherapy associated or not with rituximab or high dose zidovudine and valganciclovir should be the next step. If further relapse occurs combination chemotherapy instead of single agent therapy should be tried or IL-6 targeting therapies, but due to the lack of sufficient data in terms of IL-6 targeting therapies in HIV associated patients, this should be considered as an option for clinical trials [9].

Over the years, due to new therapeutic agents and strategies, the progression free survival and overall survival in CD patients have significantly increased [78,85]. *Talat* reported in a 2011 Castleman's disease review a three-year disease-free survival rate of 45.7%, this rate being obtained in a group of 84 HIV negative MCD patients [86]. Another study has reported a 10-years overall survival rate of approximately 40%, this study being conducted on 60 MCD patients [87]. Finally, there are also other tumors that may benefit from different strategies as the ones presented in this review [88-91].

Conclusions

Castleman's disease is a rare and complex pathology, whose etiopathogenesis is still incompletely elucidated. Over the years the overall survival and progression free survival has significantly increased, due to different therapeutic options that have emerged, options that have constantly offered better and better results.

In terms of unicentric Castleman's disease it is well known that the surgical approach offers great results with low rates of recurrence. For the patients with inoperable unicentric CD or for those who have contraindications for surgery, radiotherapy alone or followed by surgery or MCD treatment approaches should be considered.

According to literature HIV associated MCD cases should be managed with rituximab, which is associated with good results in terms of symptom control and disease progression. For the idiopathic MCD patients, IL-6 targeting therapies like siltuximab and tocilizumab have proved to be the first option. In HIV associated cases this line of treatment lacks sufficient data. Therefore, it should be limited in clinical trials for the non-responders to rituximab and chemotherapy. Corticosteroids have proven to be efficient in terms of controlling the acute B-phase symptoms, but on the long term the results are limited, with a complete remission rate that it is estimated to be less than 15%. Further investigation regarding the chemical interactions between different receptors and therapeutic molecules, understanding the mechanism of action and the potential benefits of each therapeutic agent may prove useful in clinical practice for treating CD.

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