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THE IMPACT OF 2017 GUUDELINES ON THE DIAGNOSIS OF IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE (iMCD): A LITERATURE REVIEW

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Idiopathic Multicentric Castleman Disease (iMCD), a disease of unknown etiology is characterized by angiofollicular hyperplasia. Many of its features, attributed to the overactivity of interleukin 6 (IL-6), can be seen in other conditions such as diseases of inflammatory, infectious or neoplastic nature. Until the introduction of the diagnostic guidelines for iMCD, the reported literature included numerous cases of seemingly mixed presentation. To avoid misdiagnoses, diagnostic criteria was approved in March 2017 by experts from different fields including hematology, oncology, and rheumatology. The diagnosis of iMCD requires the exclusion of multiple conditions that can present in a similar manner. However, the process of exclusion is not always straightforward. We carried out a literature review to gauge the impact of the new criteria with respect to diagnostic accuracy, exclusion of mimicking conditions and reported difficulties in using the above-mentioned criteria. We also reviewed the latest trends in the treatment of iMCD using the collected data. A total of 39 cases were identified. 76% of the cases (n=30) reported successful application of the full diagnostic criteria. Only 24% (n=9) cases were reported with overlapping conditions suggesting unsuccessful use of exclusion criteria. Tocilizumab was the most commonly used therapeutic agent in 46.1% (n=18) of the cases followed by rituximab, sirolimus, and siltuximab. The majority of the physicians diagnosed iMCD accurately and described minimal to no difficulties in applying the diagnostic criteria. Also, the majority of the patients responded well to therapies targeting IL-6 in addition to other immunomodulatory/immunosuppressive agents.

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INTRODUCTION

Castleman disease (CD) is a rare condition of the lymphatic system characterized by proliferative changes in the lymph nodes. The unicentric and multicentric categorization is based on the number of nodal regions involved [1]. The idiopathic multicentric variant presents with features that tend to overlap with other diseases [2]. Before the introduction of the diagnostic criteria for idiopathic Multicentric Castleman Disease (iMCD), the disease was frequently reported in association with conditions that now need to be excluded for making a diagnosis [2]. While the new guidelines made the accurate diagnosis of iMCD possible, it can be challenging to exclude certain conditions with confidence specifically when the disease is obviously present. Hence, cases of iMCD can still be seen in literature being reported with simultaneous occurrence of other conditions, like systemic lupus erythematosus (SLE) [3-11]. The aim of our review was to analyze the cases of iMCD reported after the introduction of the diagnostic criteria and gauge the impact of these criteria on the ability to make a successful diagnosis. Particularly, cases of overlap being reported, and any difficulty reported while using the criteria for diagnosis and exclusion. Also, we were interested in seeing the latest trends in the treatment of iMCD [12].

REVIEW

MATERIAL & METHODS

PubMed Central (PMC), EMBASE, and MEDLINE databases were searched for the collection of published records using a comprehensive list of MESH terms and boolean operators. After careful review of citations, duplicate articles were removed. A total of 198 records were identified. Of those, 60 records were selected using the automated tag filter of “case report” and “case series”. Inclusion and exclusion criteria **(Table 1)** were applied to the remaining articles. 13 out of the 60 articles were excluded because the primary diagnosis was not iMCD. 47 reports were sought for data retrieval. 6 of those were excluded since the diagnosis was either not histologically confirmed or specified in the article. 2 cases of iMCD associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes) were also excluded. The remaining 39 articles and any additional information attached were analyzed thoroughly to gather the data **(Figure 1).**

Inclusion Criteria

Case reports and case series from April 01, 2017, until July 31, 2021

Histologically confirmed cases of idiopathic multicentric Castleman disease and its subtypes (TAFRO, NOS)

Articles published in the English language, or English translation provided by the author

Exclusion Criteria

Unicentric Castleman Disease (UCD), Human Herpesvirus-8-associated Multicentric Castleman Disease, Multicentric Castleman Disease associated with POEMS syndrome

Diagnosis not confirmed histologically or not specified

Table 1: Inclusion and exclusion criteria used for the analysis of the articles

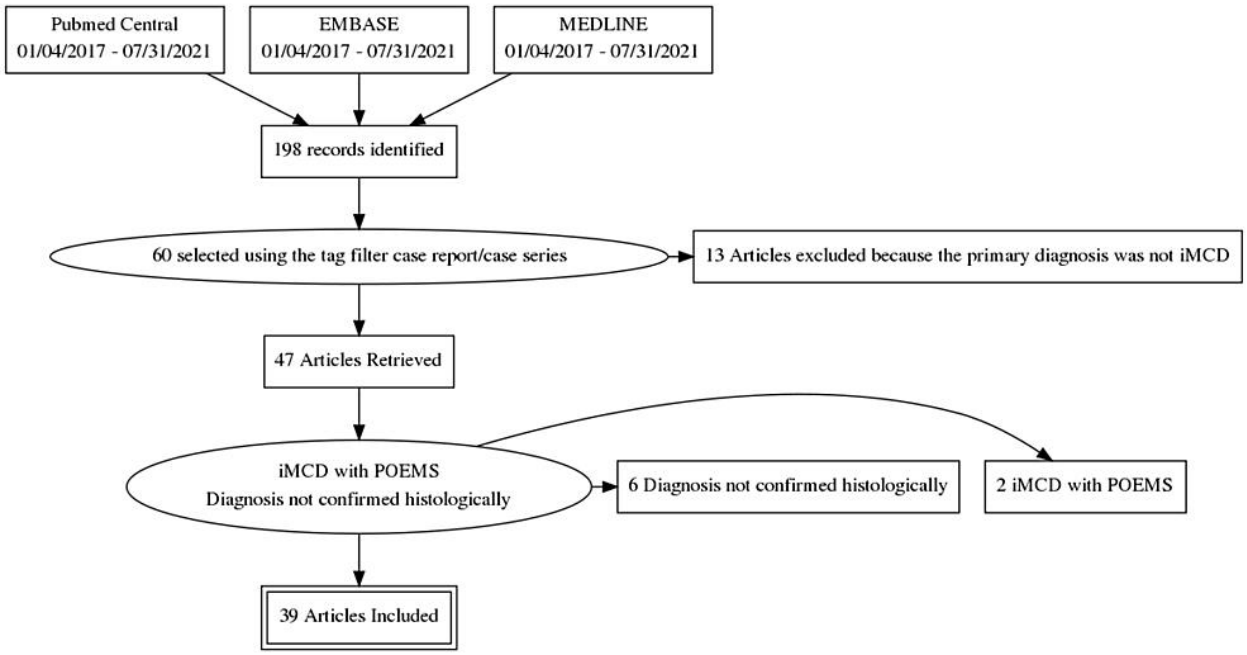

Figure 1: PRISMA Flow Diagram

RESULTS

Of the total 39 cases, 23 were male (59%) and 15 were female (38.4%). The majority of the patient population was of Caucasian ethnicity (30.8%) and 9 were of Asian origin. Ethnicity was not specified for 14 patients. The median age at diagnosis was 44 years with a range of 2 - 82 years. The mean time to presentation and diagnosis was 5.39 months. 22 of the patients were diagnosed with iMCD-NOS and 17 with iMCD subtype TAFRO syndrome. The diagnostic criteria were successfully applied in 30 cases [8,13-37] while the remaining 9 cases [3-11] faced some difficulty in the diagnostic process. These 9 cases either failed to apply the exclusion criteria or/and reported iMCD with a disease that must have been excluded. Tocilizumab was the most commonly prescribed therapeutic agent in 46.1% (n=18) of the cases. However, half of these patients (n=9) failed to achieve remission with tocilizumab. Rituximab was the second most prescribed agent at

25.6% (n=10) followed by sirolimus in 20.5% (n=8) and siltuximab in 12.8% (n=5) of the cases. Combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) was instituted in 15.4% (n=6) of the cases. Apart from corticosteroids, more than one agent was used in 41% (n=16) of the patients. Corticosteroid usage as a single agent or in combination was noted in 71.8% (n=28) of the analyzed cases. The response to treatment was relatively higher among analyzed cases. 84.6% (n=33) of the patients were reported to have achieved full remission. Only 3 cases were reported with failure of the treatment. 3 of the patients died unfortunately while receiving the treatment. One of the articles had no mention of the response to treatment. The most common histological subtype was plasma cell type (53.8%, n=21) followed by hyaline vascular (30.8%, n=12) and mixed (15.4%, n=6) subtypes. The findings are summarized in **Table 2.**

Parameter	Total	Parameter	Total
Gender		*Histological Subtype*	
Male	59% (n=23)	Plasma Cell Type	53.8% (n=21)
Female	38.5% (n=15)	Hyaline-vascular	30.8% (n=12)
Not Specified	2.6% (n=1)	Mixed	15.4% (n=6)
Age (years)		*Autoantibodies reported in association with iMCD*	
Median	44	ANA	20.5%
Mean	43.42	Anti-RNP	5.12%
Range	02 – 82	Miscellaneous	12.8%
Ethnicity		*Cases reporting overlapping diseases or difficulty with diagnostic criteria*	N=09
Asian	23%		
Caucasian	30.8%	*Therapeutic agents used*	
Miscellaneous	5.2%	Tocilizumab	46.1% (n=18)
Not Specified	41%	Rituximab	25.6% (n=10)
		Sirolimus	20.5% (n=8)
Time to presentation (months)		Siltuximab	12.8% (n=5)

Mean	5.39	Combination chemotherapy (CHOP)	15.4% (n=6)
Range	0.25 – 36	Overall corticosteroid usage	71.8% (n=28)
Primary Diagnosis		*Outcome*	
iMCD-NOS	56.4% (n=22)	Remission	84.6% (n=33)
iMCD-TAFRO	43.6% (n=17)	No Response	7.7% (n=3)
		Deceased	7.7% (n=3)

Table 2: Summary of findings in tabulated form

ANA antinuclear antibody

Anti-RNP anti-ribonucleoprotein antibody

iMCD-NOS idiopathic multicentric Castleman disease not otherwise specified

iMCD-TAFRO idiopathic multicentric Castleman disease with thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly

DISCUSSION

Castleman disease is a rare systemic disorder characterized by angiofollicular lymph node hyperplasia. The disease can present with clinical and histopathologic features that tend to overlap with other well-known hematological, oncological, rheumatological, and virological conditions [2]. The underlying pathophysiology involves overexpression of interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and increased activity of follicular dendritic cells. Castleman disease is classified into two subtypes based on the number of nodal regions involved. Unicentric Castleman disease (UCD) has lymph node(s) involved in a single region while multicentric Castleman disease (MCD) involves lymph nodes in more than one region of the body. MCD is further classified into two types based on the association with Human Herpesvirus 8 (HHV-8) infection [38]. HHV-8 associated MCD is secondary to HHV-8 infection in HIV-positive or immunocompromised patients. Of all the types of Castleman disease, the HHV-8 associated variant has a clear etiology. HHV-8 negative disease is classified as idiopathic multicentric Castleman disease (iMCD).

The etiology of iMCD is unknown. However, several driving factors have been proposed, including autoimmune, autoinflammatory, neoplastic, and infectious agents other than HHV-8

[39]. This necessitates the exclusion of such diseases before making a diagnosis of iMCD. Based on the proposed etiologic factors, iMCD has two clinical subgroups:

iMCD-TAFRO syndrome: iMCD associated with thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly (TAFRO).

iMCD-not otherwise specified (iMCD-NOS): Patients with iMCD who do not have the TAFRO subtype or associated POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes) syndrome are considered iMCD-NOS. It is important to point out that POEMS syndrome co-occurs with iMCD but is not considered a subtype [2].

The major diagnostic criteria for iMCD requires the presence of typical lymph node histologic features. There are 3 histologic variants namely hyaline-vascular (HV) or Hypervascular (HyperV), plasma cell (PC) or plasmacytic, and mixed which displays features of both HV and PC [40]. The PC variant is the most common lymph node histology, followed by HV, and the mixed variant being the least common [41]. Our study showed similar findings (PC 53.8%, HV 30.8% Mixed 15.4%). It is important to note that these lymph node features are brought upon by systemic hypercytokinemia. The cytokine storm can be associated with other conditions resulting in Castleman-like lymph node features and mimic iMCD [41]. Hence the exclusion criteria make an important part of the diagnostic criteria for iMCD. The diagnosis of iMCD requires 2 major and 2 minor criteria to be met in addition to meeting all the exclusion criteria [2]. As stated above, several conditions may present with features suggestive of iMCD and result in misdiagnosis. Some of the conditions are highlighted in table 3 and it is important to keep these in the list of differentials during the diagnostic and therapeutic process.

Infectious disorder	Autoimmune diseases	Malignant or Lymphoproliferative disorders
Human Herpesvirus-8	Systemic lupus erythematosus	Hodgkin and non-Hodgkin lymphoma
Infectious mononucleosis or chronic EBV infection	Rheumatoid arthritis	Multiple myeloma
Cytomegalovirus	Adult-onset Still disease	Primary lymph node plasmacytoma
Toxoplasmosis	Juvenile idiopathic arthritis	Follicular dendritic cell sarcoma
Human Immunodeficiency Virus	Autoimmune lymphoproliferative syndrome	POEMS syndrome
Tuberculosis		

Table 3: Diseases to exclude before making a diagnosis of iMCD

POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein, skin changes

The autoimmune diseases from the exclusion criteria are associated with antibodies but the presence of these antibodies does not imply the exclusion of iMCD. The diagnosis of these diseases should be based on following the full diagnostic criteria for these diseases, not just on the detection of the autoantibodies [2]. This is because patients of iMCD can have autoantibodies but not meet the rest of the criteria for an autoimmune condition like SLE [2]. In such a case the diagnosis would be that of iMCD and not the autoimmune disease. In our study the most frequently reported antibodies were ANA (20.5%) and anti-RNP (5.12%).

Given the non-specific presentation and the tendency to overlapping features, iMCD can pose a diagnostic dilemma. Implementing the diagnostic criteria could prove challenging specifically when the disease is first encountered. Nonetheless, it is encouraging that the majority of the cases (30) reported minimal to no difficulties [8,13-37], and most of them made an accurate diagnosis. Only 9 of the cases mentioned facing difficulty and/or reported co-occurrence of iMCD with one of the diseases that should have been excluded as per the diagnostic criteria. The details and stated difficulties of those cases are presented in table 4.

Author/Year	Study	Difficulty	Diagnosis	Overlapping disease reported
Kawano M et al. [6] 2021	HHV-8-negative multicentric Castleman disease patients with serological, histopathological and imaging features of IgG4-related disease	iMCD could not be ruled out to make a single diagnosis of IgG4 Related Disease (IgG4-RD)	iMCD overlap with IgG4-RD	IgG4 Related Disease
Puerta G et al. [4] 2021	TAFRO syndrome mimicking systemic lupus erythematosus: Case report and literature review	The patient met diagnostic criteria for SLE but did not respond to standard SLE treatment	iMCD-TAFRO	Systemic Lupus Erythematosus
Endo Y et al. [7] 2021	Idiopathic multicentric Castleman disease with novel heterozygous Ile729Met mutation in exon 10 of familial Mediterranean fever gene	Previously diagnosed with IgG4 Related Disease	iMCD overlap with IgG4-RD	IgG4 Related Disease
Ducoux G et al. [8] 2020	Thrombocytopenia, Anasarca, Fever, Reticulin Fibrosis/Renal Failure, and Organomegaly (TAFRO) Syndrome with Bilateral Adrenal	Initial confusion with SLE and antiphospholipid syndrome	iMCD-TAFRO overlap with Sjogren syndrome	Sjogren syndrome

	Hemorrhage in Two Caucasian Patients			
Alhoulaiby S et al. [11] 2020	Castleman disease and SLE in a G6PD-deficient Marfan patient: a case report and literature review	Difficulty with ruling out SLE or iMCD	iMCD overlap with SLE	Systemic Lupus erythematosus
Zapata S et al. [5] 2019	Idiopathic multicentric Castleman's disease, infrequent cause of Lupus-like. Case Report	Initially diagnosed and treated as SLE and secondary Sjogren	iMCD	SLE Sjogren syndrome
Baker TS et al. [3] 2018	A novel FAS mutation with variable expressivity in a family with unicentric and idiopathic multicentric Castleman disease	Could not conclusively rule out Autoimmune Lymphoproliferative Syndrome (ALPS)	iMCD overlap with ALPS	Autoimmune Lymphoproliferative Syndrome
Dei-Adomako YA et al. [9] 2018	Sjogren's and plasma cell variant Castleman disease: a case report	N/A	iMCD overlap with Sjogren	Simultaneous diagnosis with iMCD and Sjogren syndrome
Minemura H et al. [10] 2018	Possible Association of Multicentric Castleman's Disease with Autoimmune Lymphoproliferative Syndrome	Difficult to exclude ALPS	iMCD-TAFRO overlap with ALPS	Autoimmune Lymphoproliferative syndrome

Table 4: Cases reported with overlapping diseases

N/A not applicable

The treatment of iMCD is directed against IL-6 that is the main culprit responsible for the pathophysiology and symptomatology of the disease. Siltuximab (a monoclonal antibody against IL-6) ± corticosteroids are the recommended first-line treatment. This therapy is effective and favored for its safety profile and worldwide approval [39]. Treatment of the patients who fail siltuximab needs to be modified according to the severity of the disease [39]. Rituximab should be used as a second-line agent in patients who fail treatment with siltuximab and do not require intensive care or have progressive organ dysfunction. Rituximab can be used alone or in combination with corticosteroids and other immunomodulators [39]. In our study, rituximab was the second favorite drug after tocilizumab. Its use was reported in 10 cases with a higher remission rate. Failure of response to rituximab was reported in three out of the 10 cases. Rituximab was either used alone or as a part of the combination chemotherapy. Treatment failure with rituximab

alone warrants switching to immunomodulators/immunosuppressants as third-line agents. These patients are classified as having severe disease requiring intensive care, or have progressive organ failure. Such patients are treated with combination chemotherapy in the form of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [39]. Tocilizumab is a monoclonal antibody directed against IL-6. It has been approved and used for the treatment of iMCD in Japan since 2005 [42]. The study by Fujimoto S. et.al [43] reported the use of tocilizumab in 40-57 percent of the cases depending upon the disease severity. Our findings are similar, with tocilizumab use reported in 46.1% (n=18) of the cases, 9 of which failed to achieve remission.

Other agents used included sirolimus (n=8), cyclosporin (n=4), anakinra, and thalidomide (2 cases each), and bortezomib (n=1). These agents were used either alone or in combination with other medicines. In addition, 71.8% (n=28) of the cases reported using glucocorticoids in combination with the above-mentioned agents. Glucocorticoids constitute an important part of the treatment regimen for iMCD. These are used to reduce the symptoms of the disease and achieve remission. However, 50% of the patients fail to respond to glucocorticoids [44].

The response to treatment depends upon accurate diagnosis, disease severity, time to diagnosis, and experience of the treating physician. An international study conducted in 2018 by van Rhee, Frits et al. showed a response rate of 61% to all the therapies available for the treatment of iMCD [45]. In our study, the overall remission rate was significantly higher at 84.6% (n=33). Three patients died unfortunately while receiving the prescribed treatment. While the remaining three patients showed a partial or no response. The overall prognosis of iMCD is poor. Approximately 23%-45% of the patients die within 5 years of diagnosis, and approximately 60% die within 10 years [46].

CONCLUSION

The 2017 diagnostic guidelines for iMCD seem to be helping physicians in making an accurate diagnosis of the disease which could lead to a better understanding of the disease and successful treatment. While confusion could still be faced in a minority of cases given the nature of the disease, the majority of the physicians are reporting successful exclusion of other similar conditions. Also, tocilizumab, rituximab and siltuximab seem to be the mainstay of the treatment currently, at least until a better understanding of the disease is achieved which can lead to the development of targeted therapeutic agents.

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