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Castleman Disease, TAFRO Syndrome and Related Disorders

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ABSTRACT

Castleman B described patients with mediastinal tumors mimicking thymomas with characteristic histopathology, and this condition was named Castleman disease (CD). CD has been classified clinically as Unicentric CD (UCD) and multicentric CD (MCD). Histopathologically, CD has been classified as hyaline vascular type, plasma cell type, mixed type, hyper-vascular type, and plasmablastic type. MCD has been etiologically classified as human herpesvirus-8-related (HHV-8-related); HHV-8-unrelated, aka idiopathic MCD (iMCD); polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome-related, and others. Furthermore, iMCD has also been classified as iMCD with thrombocytopenia, anasarca, fever, reticulin myelofibrosis or renal insufficiency and organomegaly (TAFRO syndrome), and iMCD not otherwise specified. Thus far, we have discussed diseases that have been named after the renowned pathologist Castleman. However, the use of eponyms and vague disease names has contributed to confusion in understanding disorders. Recently, some eponyms and indistinct disease names have been replaced by disease-specific nomenclature. As such, the question arises as to what nomenclature should be adopted for diseases such as HHV8+MCD, iMCD-NOS, POEMS and TAFRO. For instance, iMCD could be referred to as idiopathic hyper-IL-6 syndrome with polyclonal hypergammaglobulinemia and lymphadenopathy. We have proposed more specific nomenclature for CD related-disorders, and believe that the selection of the optimal therapeutic strategy for each condition depends on accurate diagnosis.

Keywords: IL-6, HHV-8; POEMS syndrome; Anasarca; Thrombocytopenia

ABBREVIATIONS

(GC) Germinal Center; (HHV-8) Human Herpes Virus-8; (MCD) Multicentric Castleman Disease; (POEMS) Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin Changes; (VEGF) Vascular Endothelial Growth Factor; (TAFRO) Thrombocytopenia, Anasarca, Fever, Reticulin Myelofibrosis/Renal Insufficiency and Organomegaly

DESCRIPTION

In 1954, Castleman B described patients with mediastinal tumors mimicking thymomas, accompanied by lymphoid follicle hyperplasia and hyalinized vessels penetrating into the germinal centers [1,2], and the condition was named Castleman disease (CD). However, CD is not fully understood due to its rarity and diagnostic challenges. CD has been classified clinically as unicentric (localized, unicentric CD [UCD]) and multicentric (systemic, multicentric CD [MCD]). Histopathologically, CD has been classified as hyaline vascular (HV) type, plasma cell (PC) type, mixed type, hyper-vascular type, and plasmablastic type [3]. MCD has been etiologically classified as human herpesvirus 8 (HHV-8)-related; HHV-8-unrelated, aka idiopathic MCD (iMCD); POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome-related, and others [3]. iMCD was also classified as iMCD-TAFRO (thrombocytopenia, anasarca (edema, pleural effusion and ascites), fever, reticulin myelofibrosis (or renal insufficiency) and organomegaly (hepatosplenomegaly and lymphadenopathy) [3-6], and iMCD-NOS (not otherwise specified)=IPL (idiopathic plasmacytic lymphadenopathy).

TAFRO syndrome was first reported in Japan in 2010. Because the histology in lymph nodes is similar in both TAFRO syndrome

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and Castleman disease patients [7-9], TAFRO syndrome is occasionally referred to as a CD related-disorder. However, the two conditions show markedly different clinical conditions [10,11]. Rates of fever, anasarca, renal failure and mortality are significantly higher in patients with TAFRO syndrome with and without iMCD than in patients with iMCD-NOS. Laboratory findings revealed significantly higher blood urea-nitrogen, creatinine, CRP, ALP, γ-GTP, D dimer and FDP concentrations in patients with TAFRO syndrome regardless of iMCD than in patients with iMCD-NOS; whereas platelet counts and total protein and albumin concentrations were significantly lower in patients with TAFRO syndrome regardless of iMCD than in patients with iMCD-NOS. In contrast, serum IgG, IgA, and IgM concentrations were significantly higher in patients with iMCD-NOS than in patients with TAFRO syndrome regardless of iMCD. Kaplan-Meier analyses found overall survival (OS) rates of patients with TAFRO syndrome decreased rapidly within 24 months of diagnosis, by which time one-third of such patients had died. OS rates, however, showed no significant difference between patients with TAFRO syndrome who had iMCD and those who did not. In contrast, >90% of patients with iMCD-NOS were still alive at 10-years after diagnosis. Taken together, these findings suggest TAFRO syndrome with and without iMCD should be regarded as the same entity, requiring prompt diagnosis and intensive care [10,11].

Most MCD cases are classified as hyper-interleukin-6 (IL-6) syndrome. Hyper-IL-6 in MCD patients has several effects including B-cell differentiation progression and plasma cell expansion causing polyclonal hypergammaglobulinemia. Additionally, it induces production of Vascular Endothelial Growth Factor (VEGF), resulting in angiogenesis in tissue, and causes differentiation of megakaryocytes in bone marrow leading to thrombocytosis. Furthermore, hyper-IL-6 also increases production of acute inflammatory proteins, including C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA), as well as hepcidin, which inhibits iron absorption in the gastrointestinal tract and inhibits iron-recycling in the reticuloendothelial systems, causing microcytic anemia [4]. Most patients with UCD have HV histology. Patients with UCD with HV histology (UDC-HV) do not usually exhibit hyper-IL-6 syndrome and are curable by surgical resection. Therefore, UDC-HV is regarded as a separate disease entity [12,13]. This indicates that the term "Castleman disease" exclusively refers to this condition.

The terms POEMS syndrome and TAFRO syndrome were coined based on clinical conditions. While some cases with these syndromes may show lymphadenopathy with CD histology, others may not exhibit lymphadenopathy. Previously, diseases were named after the renowned pathologist Castleman, which caused confusion in understanding disorders. However, now, eponyms and vague disease names have been replaced with specific disease names. For instance, Wegener's granulomatosis is now called granulomatosis with polyangiitis (GPA) and Churg-Strauss syndrome is called Eosinophilic Granulomatosis with Polyangiitis (EGPA). Therefore, we should use disease-specific names instead of eponyms for various CD related-disorders. Regarding UCD, HHV8+MCD, iMCD-NOS, POEMS and TAFRO, we suggest specific names including idiopathic hyper-IL-6 syndrome with polyclonal hypergammaglobulinemia and lymphadenopathy for iMCD. **Table 1** contains proposed specific nomenclature for CD-related disorders.

Table 1: Eponym and proposed specific disease name

Eponym/Vague disease name	Specific disease name
Unicentric Castleman disease (UCD)	Unicentric lymphadenopathy with hyperplastic follicle, atrophic GC and hyalinized vessel penetration into GC
HHV-8+MCD	hyper-IL-6 syndrome with polyclonal lymphadenopathy associated with HHV-8
Idiopathic Multicentric Castleman Disease (iMCD)	idiopathic hyper-IL-6 syndrome with polyclonal hypergammaglobulinemia and lymphadenopathy
POEMS syndrome/Crow Fukase syndrome	Polyneuropathy with hyper VEGF dysglobulinemia
TAFRO syndrome	Hyper-inflammation syndrome with severe anasarca, thrombocytopenia and renal insufficiency

This novel classification with specific nomenclature may better inform the optimum choice of therapeutic strategy. Surgical resection is an appropriate treatment for cases with UCD-HV. Cases with hyper-IL-6 syndrome should receive anti-IL-6 therapy, such as tocilizumab (anti-IL-6 receptor antibody) or siltuximab (anti-IL-6 antibody) [14]. Cases with hyper-inflammation syndrome, such as TAFRO syndrome, require more intensive therapeutic combinations [4,11,15]. While the mortality rates are high in patients with TAFRO syndrome, a single optimal treatment strategy has not yet been established. In our retrospective study, 68 patients were treated with first-line corticosteroid therapy, and second-line treatment consisted of tocilizumab in 21 patients, cyclosporine in 14, and rituximab in eight, in addition to corticosteroids [15]. It is important to use disease specific nomenclature for each condition and select the optimal therapeutic strategy.

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CONFLICT OF INTEREST

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