

*Meeting Report*

# Castleman-Kojima Disease (TAFRO Syndrome) : A Novel Systemic Inflammatory Disease Characterized by a Constellation of Symptoms, Namely, Thrombocytopenia, Ascites (Anasarca), Microcytic Anemia, Myelofibrosis, Renal Dysfunction, and Organomegaly : A Status Report and Summary of Fukushima (6 June, 2012) and Nagoya Meetings (22 September, 2012)

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Recently, a unique clinicopathologic variant of multicentric Castleman's disease (MCD) has been identified in Japan. This disease is characterized by a constellation of symptoms, as listed in the title, and multiple lymphadenopathy of mild degree with a pathologic diagnosis of atypical CD, often posing diagnostic and therapeutic problems for pathologists and hematologists, respectively. These findings suggest that this disease represents a novel clinical entity belonging to systemic inflammatory disorders with a background of immunological abnormality beyond the ordinal spectrum of MCD. To define this disorder more clearly, Japanese participants presented clinicopathologic data at the Fukushima and Nagoya meetings. Many of the patients presented by the participants were significantly accompanied by a combination of thrombocytopenia, ascites (anasarca), pleural effusions, microcytic anemia, fever, myelofibrosis, renal dysfunction, and organomegaly (TAFRO). Multiple lymphadenopathies were generally of mild degree, less than 1.5 cm in diameter, and consistently featured the histopathology of mixed- or less hyaline vascular-type CD. Autoantibodies were often detected. However, this disease did not fulfill the diagnostic criteria for well-known autoimmune diseases including systemic lupus erythematosus. Castleman-Kojima disease and TAFRO syndrome (the favored clinical term) were proposed for this disease. The patients were sensitive to steroid and anti-interleukin-6 receptor antibody (tocilizumab), but some exhibited a deteriorated clinical course despite the treatment. The participants proposed a future nationwide survey and a Japanese consortium to facilitate further clinical and therapeutic studies of this novel disease. [*J Clin Exp Hematop* 53(1): 57-61, 2013]

**Keywords:** multiple Castleman disease, Castleman-Kojima disease, TAFRO syndrome (thrombocytopenia, ascites, myelofibrosis, renal dysfunction, and organomegaly)

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## INTRODUCTION

Since the first description by Castleman in 1956,<sup>1</sup> the conceptual view and diagnostic criteria of Castleman's disease (CD) have been continuously developed. In the 1980s, three disorders as eponyms of CD were reviewed by Frizzera : localized CD of hyaline-vascular (HV) type, localized CD of plasma cell (PC) type, and "multicentric-type" CD (MCD).<sup>2-4</sup> MCD refers to an idiopathic clinicopathologic entity characterized by a predominantly lymphadenopathic appearance consistently involving peripheral lymph nodes. This disorder is regarded as an enigmatic disease because the nodal histologic change of MCD is non-specific and can be found in the context of several clinical situations.<sup>5,6</sup> Therefore, it is important that all of the known causes of this morphology, which is now expanding, be ruled out before a diagnosis of MCD is made.

MCD was originally described to have a morphology of the PC type of CD by Frizzera *et al.*<sup>2-4</sup> However, histological findings of their series were characterized by HV-type lymphoid follicles with vascular proliferation and plasmacytosis in the interfollicular area. These histological findings should have been evaluated as the mixed type of CD described by Flendrig.<sup>7</sup> In the early 1980s, Mori *et al.* demonstrated a new clinicopathologic entity, namely, idiopathic plasmacytic lymphadenopathy (IPL), with polyclonal hyperimmunoglobulinemia showing histological findings that resemble the PC type of CD, but preserving a normal germinal center appearance in the affected nodes.<sup>8</sup> Later, Frizzera concluded that IPL is identical to MCD reported in Western countries,<sup>2,5</sup> but unfortunately he paid little attention to the significance of the morphologic difference in the germinal centers of MCD, that is, either IPL type or not. Recently, Suda *et al.*<sup>9</sup> and Kojima *et al.*<sup>10-13</sup> showed that no Japanese patients with idiopathic MCD are associated with human herpes virus 8 (HHV8), in contrast to those in Western countries. Notably, Kojima *et al.* further revealed that Japanese patients are delineated into two

distinct clinicopathologic groups on the histologic grounds of IPL type or not : IPL type is defined by prominent polyclonal hyperimmunoglobulinemia, normal germinal centers, and sheet-like infiltration of PCs in the interfollicular area of the lymph node ; and non-IPL type is characterized by female predominance, higher age group, high incidence of pleural effusion or ascites, and frequent association with autoimmune disease during the course of disease, and mixed-type or less frequently HV-type CD histology (Table 1).<sup>14,15</sup> More recently, Takai *et al.* reported three patients sharing a constellation of symptoms, namely, thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO syndrome), with HV-type histology of the lymph node in one patient.<sup>16</sup> Kawabata subsequently shed light on diagnostic and therapeutic issues of this non-IPL-type MCD at the symposium of the annual meeting of the Japanese Society for Lymphoreticular Tissue Research, which was held in Fukushima on 6 June, 2012, by President Prof. Masafumi Abe (Fukushima Medical University).<sup>17</sup> He also proposed a nosological term of TARIFA syndrome (thrombocytopenia, anemia, renal dysfunction, inflammation, myelofibrosis, and ascites) for this peculiar disease.

To define the disease, diagnostic criteria, and treatment of non-IPL-type MCD more clearly, a research meeting was organized at Nagoya University Hospital on 22 September, 2012. Hematologists and pathologists presented the cases and discussed their diagnosis and treatment. This report presents highlights from that meeting and a consensus document regarding the current understanding of this disease.

## TERMINOLOGY AND DIAGNOSIS

As described above, this novel disease is characterized by a peculiar constellation of symptoms and mixed-type or less frequently HV-type CD histology in the affected lymph nodes. The criteria for the distinction of this disease from other systemic inflammatory disorders or autoimmune dis-

**Table 1.** Disorders that manifest with Castleman's disease histology

Castleman's disease	Histologic subtypes
Primary (Idiopathic)	
Non-human herpes virus type-8-related*	IPL type
Human herpes virus type-8-related*	
Secondary	
In HIV infection	
IgG4-related disease*	
In plasma cell dyscrasia (POEMS syndrome)*	
In systemic inflammatory disease (TAFRO syndrome)*	non-IPL type
In malignant lymphomas*	

\* , prevalent in Japan ; IPL, idiopathic plasmacytic lymphadenopathy ; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes ; TAFRO, Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis, and Organomegaly ; refer to Kojima *et al.* (2008)

eases have not been clearly delineated in the literature. It is still controversial whether this disease should be subsumed into the category of MCD or constitutes a distinct entity. Meeting participants concluded that this disease can be regarded as MCD secondary to systemic inflammatory disease and that the terms Castleman-Kojima disease and TAFRO syndrome (a favored clinical term) should be provisionally applied to this disease, taking into account that none of these patients fulfills the diagnostic criteria for any of the definite autoimmune diseases.

**DEFINITION OF CASTLEMAN-KOJIMA DISEASE (TAFRO SYNDROME)**

Castleman-Kojima disease is a systemic inflammatory disorder that occurs in patients without any known autoimmune diseases or other well-defined lymphoproliferative disorders, and can involve bone marrow, pleura, peritoneum, kidneys, liver, and lymph nodes. The cause of this disease is unknown. The following criteria have been established for the diagnosis of Castleman-Kojima disease :

- ☆ Blood count abnormalities : low counts of platelets and/or red blood cells ;
  - Thrombocytopenia
  - Microcytic anemia
- ☆ Systemic inflammation : polyserositis (pleuritis/peritonitis) ; inflammation of the tissue lining the lungs or abdominal cavities
  - Pleural effusions
  - Ascites
- ☆ Renal dysfunction
- ☆ Myelofibrosis
- ☆ Immunologic disorder : rheumatoid factor, platelet-associated IgG, anti-thyroid antibody, and positivity on direct Coombs test
- ☆ Antinuclear antibody
- ☆ Rare polyclonal hyper- $\gamma$ -globulinemia : less than 4,000 mg/dL
- ☆ Laboratory data abnormalities : elevated level of alkaline phosphatase and decreased level of lactate dehydrogenase
- ☆ Elevated levels of interleukin-6 and the vascular endothelial growth factor in serum or effusions

- ☆ Lymphadenopathy : generally of mild degree (less than 1.5 cm in diameter)
- ☆ Histology of mixed-type and less frequently HV-type CD

**CLINICAL FEATURES**

Castleman-Kojima disease occurs in the middle-aged and elderly, with a median age of 56 years old and a range from 43 to 65 years old. This disease is 4 times more common in women than in men. The main clinical findings have been briefly summarized above. The patients are frequently accompanied by thrombocytopenia and may be diagnosed with idiopathic thrombocytopenic purpura. The constellation of symptoms is mandatory for a definitive diagnosis, which was first emphasized by Takai *et al.* and subsequently by Kawabata. The TAFRO and TARIFA syndromes proposed by them, respectively, are shown in Table 2. The participants in our meeting recommend modified TAFRO syndrome. A lymph node biopsy is necessary for the diagnosis and exclusion of other lymphoproliferative disorders or lymphoma. It should be noted that multiple lymphadenopathies are of mild degree, generally less than 1.5 cm in diameter. Some may lack this phenomenon. This issue should be clarified in the future. In this meeting, an elevated level of alkaline phosphatase, but not of lactate dehydrogenase, was indicated and confirmed in most of the cases, suggesting the hepatic or biliary involvement of the disease. HHV8, human immunodeficiency virus, or Epstein-Barr virus was not detected.

**MORPHOLOGY AND IMMUNOPHENOTYPE**

The lymph nodes showed numerous lymphoid follicles with atrophic germinal center. The majority of these follicles were of the small HV type and the epithelioid type with broad and concentrically arranged mantle zones. The cells of the latter type consisted mostly of follicular dendritic cells often featuring enlarged nuclei with prominent nucleoli. The interfollicular area was consistently characterized by moderate to prominent vascularity with short, closely spaced venules containing high endothelial cells. Moderate to large sheets of mature PCs were very frequently observed. Immature PCs and immunoblasts were scarce. Various numbers of small

**Table 2.** Comparison and consensus of TAFRO/TARIFA syndrome

TAFRO (Takai, 2009)	TARIFA (Kawabata, 2012)	TAFRO (Consensus in 2012)
<u>T</u> hrombocytopenia	<u>T</u> hrombocytopenia	<u>T</u> hrombocytopenia
<u>A</u> nasarca	<u>A</u> nemia, microcytic	<u>A</u> nasarca
<u>F</u> ever	<u>R</u> enal dysfunction	<u>M</u> yl <sup>o</sup> <u>F</u> ibrosis
<u>R</u> eticulin fibrosis	<u>I</u> nflammation, systemic	<u>R</u> enal dysfunction
<u>O</u> rganomegaly	<u>M</u> yl <sup>o</sup> <u>F</u> ibrosis	<u>O</u> rganomegaly
	<u>A</u> scites (Anasarca)	

lymphocytes, scattered neutrophils, and eosinophils were intermingled with PCs. Plasmacytoid monocytes were undetected. The preferred histopathologic diagnoses were mixed type and less frequently HV type.

The immunoglobulin light-chain reactivity of PCs was polyclonal with a  $\kappa$  to  $\lambda$  ratio of 2 : 1. Heavy-chain antigens were predominantly Ig $\lambda$  and IgA, but less commonly IgM. CD57<sup>+</sup> follicular T-cells were hardly seen in the affected germinal centers. The tight/concentric or expanded/disrupted pattern of the follicular dendritic cell network was intensely highlighted with monoclonal antibody 2G9 and CNA 42.

## PROGNOSIS AND THERAPEUTIC APPROACHES

Many of the patients had a prolonged indolent clinical course, and were sensitive to high-dose steroid treatment and anti-interleukin-6 receptor antibody (tocilizumab), but appeared to have a lower complete remission rate than those with IPL-type MCD. Some may show a rapidly deteriorated clinical course. There was no consensus on good therapeutic approaches for them.

## CONCLUSIONS

The lack of understanding of currently ill-defined disorders affecting multiple organs is aggravated by confusion in the literature regarding terminology and diagnostic criteria for individual disease entities and clinical syndromes. It is already well known that idiopathic MCD among Japanese patients is unique in its HHV8 negativity and chronic clinical processes compared with that in Western countries.<sup>9-13</sup> Kojima *et al.* first indicated that idiopathic MCD consisted of two main subgroups, IPL and non-IPL types, with distinct clinicopathological findings. They clearly described that non-IPL-type MCD is characterized by female predominance, older age, high incidence of pleural effusion or ascites, and frequent association with autoimmune disease during the course, although IPL type has been relatively well described in the literature.<sup>14,15</sup> The histopathological findings bear some resemblance to those of MCD cases in Western countries. However, interestingly, the clinical course is generally quite different between Japanese and Western patients with non-IPL-type MCD. The chronic indolent clinical course of the former is evidently contrasted with a very aggressive one in the majority of cases of the latter.

In recent years, an increasing number of case reports have been published on this constellation of symptoms. Takai *et al.*<sup>16</sup> and Kawabata<sup>17</sup> proposed the nosological terms of TAFRO and TARIFA syndromes. This disease now poses serious diagnostic and therapeutic challenges for pathologists and clinicians, including the differential diagnosis from other autoimmune diseases, because it remains to be elucidated how many or what combination of symptoms or findings is manda-

tory for the diagnosis of this peculiar disease.

The meeting participants concluded that the terms Castleman-Kojima disease and TAFRO syndrome currently modified should be applied to this systemic inflammatory disorder in cases not categorized as any other known disease. The participants also proposed the establishment of a consortium to collect further clinical outcome data and to promote a nationwide survey on Castleman-Kojima disease and related disorders. It is hoped that these studies will recognize new clinicopathologic aspects involved in the diagnosis and pathogenesis of this disorder and lead to multicenter clinical trials to evaluate novel therapies for this disease.

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