TAFRO Syndrome

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KEYWORDS

• TAFRO syndrome • Castleman disease • Clinical features • Pathogenesis

KEY POINTS

- TAFRO syndrome is a newly recognized variant of idiopathic multicentric Castleman disease (iMCD) that involves a constellation of syndromes: thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O).
- Thrombocytopenia and severe anasarca accompanied by relatively low serum immunoglobulin levels are characteristic clinical findings of TAFRO syndrome that are not present in iMCD–not otherwise specified (iMCD-NOS).
- Lymph node biopsy is recommended to exclude other diseases and to diagnose TAFRO syndrome, which reveals characteristic histopathological findings similar to hyaline vascular-type Castleman disease.
- TAFRO syndrome takes a more aggressive course than iMCD-NOS.
- The main therapeutic options include corticosteroids, immunosuppressive therapy (eg, cyclosporin A), rituximab or rituximab-based therapy, and anti-interleukin-6 therapies (eg, tocilizumab and siltuximab).

INTRODUCTION

TAFRO syndrome is a recently recognized systemic disease that was initially identified by Takai and colleagues in 2010.[1] The investigators reported 3 cases that shared characteristic clinical symptoms, which included thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O).[1] Only 1 of the 3 patients underwent lymph node biopsy, and the specimen exhibited histologic features similar to those of Castleman disease (CD). Thus, Takai and colleagues suggested that TAFRO syndrome might be a unique variant of CD.

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CD is a rare and poorly understood lymphoproliferative disorder that was originally described by Castleman and colleagues in 1956.[2] This disorder consists of heterogeneous diseases that share several histopathological findings, and can be histologically divided into hyaline vascular (HV)-type or plasma cell (PC)-type CD.[3] Cases of HV-type CD exhibit interfollicular vascular proliferation that often penetrates the atrophic germinal centers, whereas PC-type CD generally exhibits expanded intrafollicular areas with sheets of mature plasma cells.[4,5] The germinal centers of PC-type CD can be hyperplastic or atrophic, and the hyalinized vessels and follicular dendritic cell dysplasia that are seen in HV-type CD are not observed in PC-type CD.[4,6] However, HV-type CD also exhibits findings that are characteristic of PC-type CD and vice versa.[4,7] The overlapping features of CD sometimes make it difficult to differentiate between the 2 histologic types, and these cases are referred to as mixed-type CD.[4,7]

CD cases that involve solitary or multiple lymph node regions are classified as unicentric CD (UCD) and multicentric CD (MCD), respectively.[4,8] Patients with UCD typically have a single asymptomatic enlarged lymph node with histologic features of HV-type CD, whereas patients with MCD present with multifocal lymph node swelling and histologic features of PC-type CD.[5,7,9] HV-type CD features are also observed in cases of MCD.[7,9] Patients with MCD experience a more progressive course, compared with patients with UCD, and MCD cases are accompanied by systemic manifestations, such as fever with abnormal laboratory findings (eg, anemia, thrombocytosis, polyclonal hypergammaglobulinemia, and elevated acute phase protein levels).[7,9]

As CD is defined according to common histopathological findings, it includes heterogeneous disorders with overlapping clinicopathological manifestations. It is now understood that MCD encompasses a heterogeneous group of systemic inflammatory disorders caused by hypercytokinemia (ie, involving interleukin [IL]-6).[4,9] Human herpes virus (HHV)-8 is a known etiologic agent that causes MCD by producing a viral homolog of IL-6, especially in immunocompromised cases (eg, patients who are infected with the human immunodeficiency virus).[10,11] To date, the etiology of non–HHV-8 MCD has remained unknown, with these cases collectively referred to as idiopathic MCD (iMCD) (**Fig. 1**).[12] MCD in Western countries was often thought to be caused

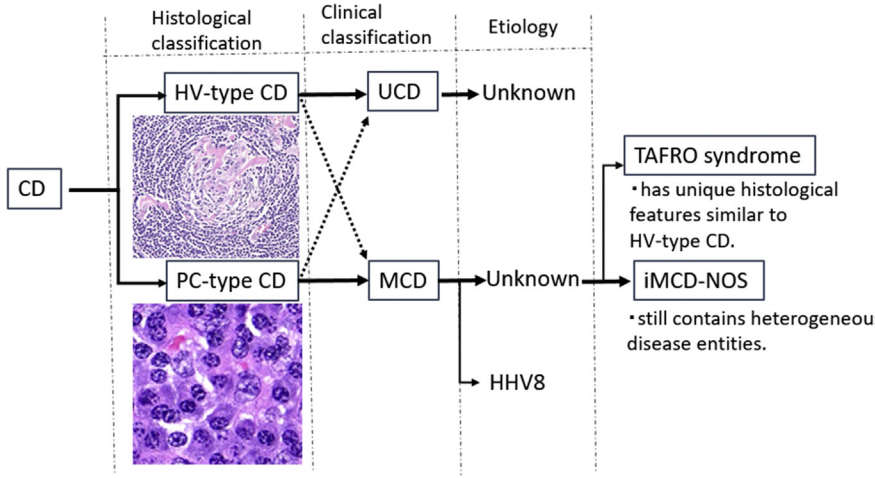

Fig. 1. Relationship between CD and TAFRO syndrome.