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Case Study

Thrombocytopenia with Reticulin Fibrosis Accompanied by Fever, Anasarca and Hepatosplenomegaly : A Clinical Report of Five Cases

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We report five cases that presented with high fever, anasarca, hepatosplenomegaly and severe thrombocytopenia with reticulin fibrosis of the bone marrow. The constellation of symptoms is not compatible with any known disease, and we had difficulty in diagnosis and treatment. The age distribution was from 47 to 56 years, and two men and three women were affected. Two patients needed hemodialysis because of renal dysfunction and oliguria with massive pleural effusion. Laboratory examinations showed normal immunoglobulin levels and no monoclonal protein. None of them showed diagnostic autoantibodies for any autoimmune diseases. Histological examination of the liver in three patients and spleen in two showed non-specific findings. Lymphadenopathy was tiny and lymph node biopsy was carried out in only one case. Histologically, paracortical hyperplasia with vascular proliferation and atrophic germinal centers resembling hyaline-vascular-type Castleman's disease or POEMS syndrome were detected. Without a definitive diagnosis, treatment was started with cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (CHOP) regimen in one patient, semi-pulse therapy with methylpredonisolone in three and cyclosporin A in three. Two patients achieved complete remission, two were steroid-dependent and the remaining one died of multiple organ failure. These findings suggest that this disease may be a novel clinical entity belonging to systemic inflammatory disorder with a background of immunological abnormality or a unique variant of multicentric Castleman's disease. 〔*J Clin Exp Hematop 53(1): 63-68, 2013*〕

Keywords: thrombocytopenia, reticulin fibrosis, anasarca, hyaline-vascular type, multicentric Castleman's disease

INTRODUCTION

We experienced five cases of severe thrombocytopenia with mild bone marrow fibrosis accompanied by high fever, anasarca and hepatosplenomegaly. Histological findings of the liver and spleen were non-specific. Because of a subtle degree of lymphadenopathy, hyaline-vascular (HV)-type Castleman-like histology of the lymph node was obtained in only one case.

The constellation of these symptoms and laboratory findings is non-specific and not compatible with any known autoimmune diseases or well-defined lymphoproliferative disorders (LPD). We report their clinical features for discussion of the possibility that this disease may be a novel clinicopathological entity or a variant of multicentric Castleman's disease (MCD).

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CASE REPORTS

Case 1

A 47-year-old woman was admitted to a local hospital because of high fever refractory to antibiotic treatment in May 2000. Severe thrombocytopenia, edema, massive pleural effusion and ascites appeared progressively, and computed tomography (CT) scan showed hepatosplenomegaly and ascites (Fig. 1A, 1B). The bone marrow could not be aspirated, and the biopsy was difficult due to massive ascites. Because her general condition deteriorated rapidly, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (CHOP) therapy was started with the suspicion of hematological malignancy, especially splenic lymphoma. Her symptoms improved slowly after the treatment with prednisolone (PSL) at 60 mg/day following one cycle of CHOP.

Because of marked elevation of alkaline phosphatase (ALP) level, she underwent cholecystectomy and liver biopsy, which revealed simple gallstone and non-specific histology of

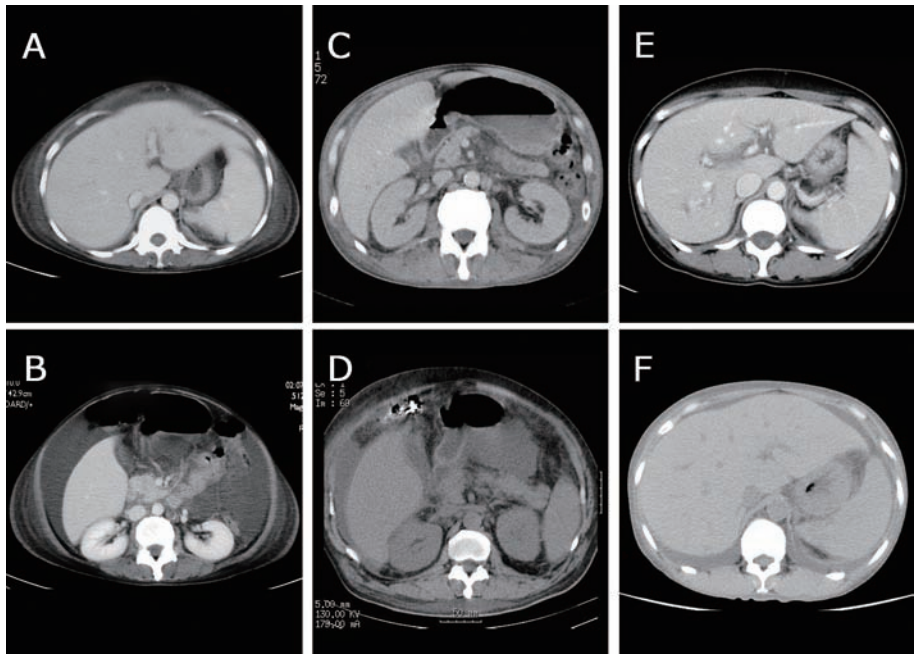

Fig. 1. Computed tomography scans of the abdomen show marked ascites, a mild degree of hepatosplenomegaly and tiny lymphadenopathy of the para-aortic region. (*1A* & *1B*) case 1 upon first admission. (*1C*) case 2, (*1D*) case 3, (*1E*) case 4, (*1F*) case 5.

the liver without lymphoma or primary biliary cirrhosis. Because she suffered from high fever, abdominal distension and thrombocytopenia again with tapering of PSL to 10 mg/day, she was referred to our hospital in December 2000.

Laboratory findings on admission (Table 1A, 1B) revealed thrombocytopenia, elevation of ALP, C-reactive protein (CRP) and hypoalbuminemia. The diagnostic autoantibodies examined were all negative, except for antinuclear antibody (ANA). The bone marrow biopsy showed proliferation of megakaryocytes and reticulin fibrosis without malignant cells (Fig. 2A, 2B). Her condition improved slowly with the continuation of PSL at 60 mg/day, but she relapsed four times with tapering of PSL to a dose of 10 mg/day or less. She is now in remission with a maintenance dose of PSL of 3 mg/day.

Case 2

A 56-year-old man was referred to our hospital because of thrombocytopenia in June 2007. He was diagnosed with immune thrombocytopenic purpura (ITP) according to the increased megakaryocytes of the bone marrow and elevated level of platelet-associated IgG (PA-IgG). Soon after the eradication treatment of *Helicobacter pylori*, he suffered from progressive edema. He was admitted to our hospital with the diagnosis of rapidly progressive glomerulonephritis because of fever, renal dysfunction with proteinuria and a high level of CRP.

Neither treatment with semi-pulse therapy of methyl-PSL (500 mg/day for three days) nor high-dose immunoglobulin therapy was effective for the severe thrombocytopenia and renal dysfunction with oliguria. He needed frequent platelet transfusions and hemodialysis. CT scan showed pleural effusion, ascites, mild degree of hepatosplenomegaly and lymphadenopathy of the para-aortic region (Fig. 1C). Splenectomy and biopsy of the liver and peritoneum revealed non-specific histological findings of the spleen, liver and peritoneum, and severe thrombocytopenia persisted.

The bone marrow biopsy revealed increased megakaryocytes and reticulin fibrosis (Fig. 2C, 2D). Increased platelet-associated anti-GPIIb/ IIIa antibody (14.8 U, ELISA method ; normal range < 3.3 U) and elevated percentage of reticulated platelets (4.3%, normal range 0.7～3.0%) were compatible with ITP, but markedly increased plasma thrombopoietin level (1,218.0 pg/mL, normal range < 142 pg/mL) was atypical of it.[1]

Immunosuppressive therapy with cyclosporin A (CsA) was started, and thrombocytopenia, edema and ascites improved slowly over the next month. His remission has been sustained even after the discontinuation of CsA in July 2008.

Case 3

A 49-year-old man was referred to our hospital because of

Table 1A. Laboratory findings

Case No.	1	2	3	4	5
Age/Sex	47/F	56/M	49/M	53/F	56/F
White blood cell (10^3/L)	8.7	10.3	12.3	8.1	5.7
Red blood cell (10^6/L)	3.8	3.45	4.08	4.02	3.63
Hemoglobin (g/dL)	10.9	10.7	11.7	12.4	9.8
Platelet (10^3/L)	15	19	10	38	44
APTT (sec)	38.4	47.1	45.7	48	28.1
PT-INR	1.04	1.27	1.36	1.26	0.94
Fibrinogen (mg/dL)	834	552	777	991	532
FDP (g/mL)	18.7	14.2	22.3	24.7	42.2
AST (IU/L)	17	13	37	28	19
ALT (IU/L)	14	8	18	19	14
Alkaline phosphatase (IU/L)	1,258	390	756	1,696	242
Lactate dehydrogenase (IU/L)	387	215	289	274	236
Total bilirubin (mg/dL)	1.5	0.7	0.7	1.9	0.4
Total protein (g/dL)	5.9	6.6	5.2	6.3	4.8
Albumin (g/dL)	2.2	2.4	2.1	2.7	2.3
Creatinine (mg/dL)	0.7	1.9	0.9	0.7	1.53
Uric acid (mg/dL)	6.1	8.9	7.4	4.4	9.1
Proteinuria	(1+)	(3+)	(−)	(1+)	(1+)
Hematuria	(2+)	(3+)	(−)	(−)	(2+)

APTT, activated partial thromboplastin time ; PT-INR, prothrombin time-international normalized ratio ; FDP, fibrin/fibrinogen degradation products ; AST, aspartate aminotransferase ; ALT, alanine transaminase

Table 1B. Serological findings

Case No.	1	2	3	4	5
C-reactive protein (mg/dL)	18.27	16.35	16.42	31.6	6.35
IgG (mg/dL)	1,046	863	1,057	1,379	707
IgA (mg/dL)	189	127	204	290	76
IgM (mg/dL)	33	82	97	38	27
Platelet-associated IgG (ng/10^7 cells)	> 300	320	300	n.d.	21.9
Anti-nuclear antibody	160	< 40	< 40	160	< 40
Anti-DNA antibody (IU/mL)	1	< 2	< 2	< 2	n.d.
CH50 (U/mL)	45.2	n.d.	32.7	51	64
PM3-ANCA (EU) (U/mL)	< 10	< 10	< 10	< 1.3	< 1.0
MPO-ANCA (EU) (U/mL)	< 10	< 10	< 10	< 1.3	< 1.0
Anti-mitochondria antibody	< 20	(−)	(−)	< 20	n.d.
Ferritin (ng/mL)	228.4	402.2	345.3	280.5	180
sIL-2R (U/mL)	730	1,150	3,300	1,341	1,560
Interleukin-6 (pg/mL)	n.d.	7.2	64.9	32	9.05
VEGF (pg/mL)	285	31	104	n.d.	188
EBV EA-DR IgG	10	< 10	< 10	n.d.	n.d.
EBV VCA IgM	< 10	< 10	< 10	< 10	< 10
EBV VCA IgG	160	160	320	80	80
EBV EBNA	40	20	80	40	80

sIL-2R, soluble interleukin-2 receptor ; PM3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibody ; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody ; VEGF, vascular endothelial growth factor ; EBV EA-DR, Epstein-Barr virus, early antigen-diffuse and restricted antibody ; EBV VCA, Epstein-Barr virus, viral capsid antigen antibody ; EBV EBNA, Epstein-Barr virus, nuclear antigen antibody ; n.d., not done. Normal range : sIL-2R 220-530 U/mL ; interleukin-6, < 4.0 pg/mL ; VEGF < 115 pg/mL

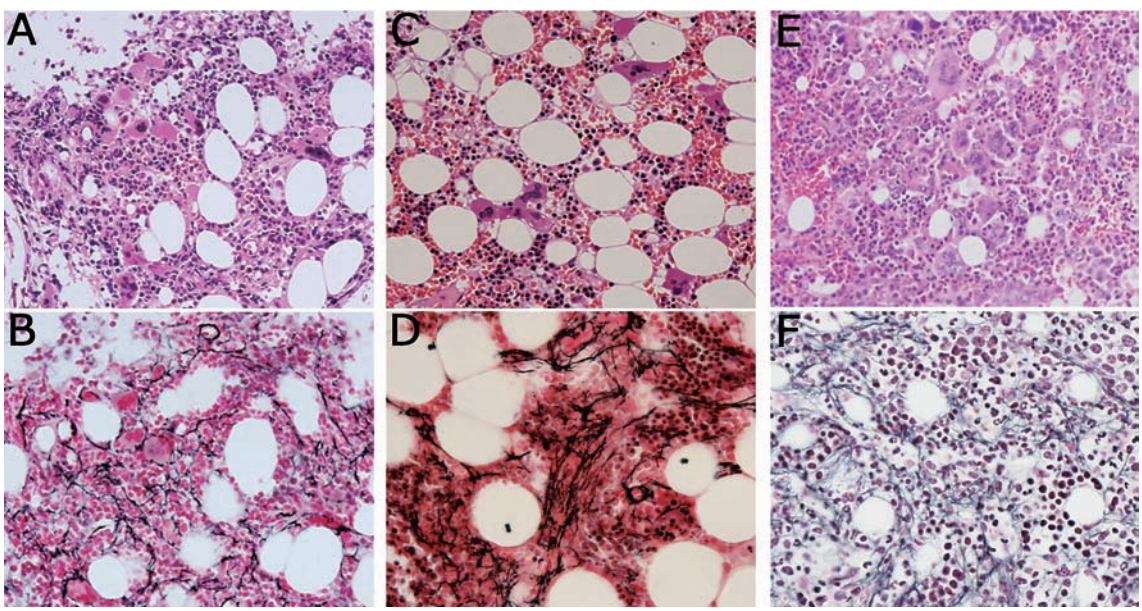

Fig. 2. Histology of the bone marrow biopsy shows increase of megakaryocytes (*2A, 2C* & *2E* ; H&E stain) and mild reticulin fibrosis (*2B, 2D* & *2F* ; silver stain). (*2A* & *2B*) case 1, (*2C* & *2D*) case 2, (*2E* & *2F*) case 5.

high fever, pleural effusion and ascites, edema and severe thrombocytopenia in August 2007. Laboratory findings on admission (Table 1A, 1B) showed severe hypoalbuminemia, elevated level of ALP, CRP and PA-IgG, but the specific autoantibodies examined were all negative.

The bone marrow could not be aspirated, and a biopsy revealed proliferation of megakaryocytes and fine reticulin fibrosis. CT scan revealed massive pleural effusion, ascites, mild hepatosplenomegaly and systemic lymphadenopathy of less than 1 cm in diameter (Fig. 1D). Histological examination of the right inguinal lymph node showed paracortical hyperplasia with vascular proliferation, and atrophic germinal centers resembling the histology of HV-type Castleman's disease (Fig. 3).

Neither treatment with semi-pulse therapy of methyl-PSL nor high-dose immunoglobulin therapy was effective for his symptoms, and he died of multiple organ failure 42 days after admission. Autopsy revealed hemophagocytic histiocytosis in the bone marrow, spleen and lymph nodes, and cytomegalovirus (CMV) infection in both lungs, esophagus, bone marrow, left adrenal gland and pancreas. These findings were assumed to be complications of immunosuppressive therapy.

Case 4

A 53-year-old woman was admitted to our hospital because of fever, hepatosplenomegaly and marked elevation of ALP and CRP in October 2011. CT scan revealed a moderate degree of hepatosplenomegaly (Fig. 1E), edematous wall of gallbladder and ascites. Histological examination of the liver showed mild infiltration of lymphocytes and mild fibrosis in the portal areas, which were non-specific findings. The autoantibodies examined were all negative, except for ANA. Serum IL-6 level increased to 32.0 pg/mL (normal < 4.0 pg/mL, Table 1B).

Progressive thrombocytopenia appeared and the bone marrow biopsy revealed increased megakaryocytes and reticulin fibrosis. Treatment with PSL was effective for fever, but edema and thrombocytopenia persisted. Although the platelet count increased to a normal level after splenectomy, the tapering of PSL resulted in the repeated exacerbation of edema. CsA was not effective, but pulse therapy of cyclophosphamide was effective to reduce the maintenance dose of PSL.

Case 5

A 56-year-old woman was admitted to our hospital because of generalized edema, oliguria, hypoalbuminemia and thrombocytopenia in April 2012. CT scan showed pleural and pericardial effusion, ascites, a mild degree of hepatosplenomegaly (Fig. 1F) and systemic lymphadenopathy of less than 1 cm in diameter. Thrombocytopenia was exacerbated, which required frequent platelet transfusions. The bone marrow could not be aspirated, and its biopsy revealed increased megakaryocytes and reticulin fibrosis (Fig. 2E, 2F). Hemodialysis was introduced because of oliguria and massive pleural effusion with respiratory failure on the sixth hospital day. The treatment with semi-pulse therapy of methyl-PSL was followed by CsA.

The patient was complicated with CMV infection, which was successfully treated with gancyclovir. She was released from hemodialysis on the 31st hospital day, and thrombocytopenia, pleural effusion and ascites improved slowly. She is now in remission with a small maintenance dose of PSL and CsA.

DISCUSSION

The ages of the five patients ranged from 47 to 56 years, and two men and three women were affected. Their common symptoms and laboratory findings are listed in Table 2. They showed a constellation of non-specific symptoms, namely, severe thrombocytopenia, anasarca, fever, reticulin fibrosis of the bone marrow and organomegaly (hepatosplenomegaly),

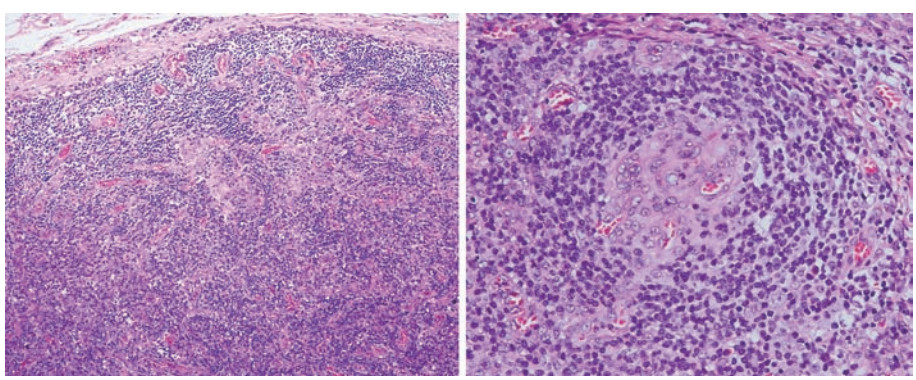

Fig. 3. Histology of the lymph node biopsy of case 3 shows paracortical hyperplasia with vascular proliferation (*left*), and atrophic germinal center resembling hyaline vascular-type Castleman's disease (*right*). Hematoxylin-eosin stain.

Table 2. Common clinical features and laboratory findings

Clinical features
Persistent fever refractory to antibiotic therapy (Fever)
Marked pleural effusion, ascites and edema (Anasarca)
Mild hepatosplenomegaly and lymphadenopathy (Organomegaly)
Laboratory findings
Severe thrombocytopenia and mild anemia
Marked hypoalbuminemia and normal immunoglobulin level
Elevated level of C-reactive protein
Increased platelet-associated IgG
Elevated level of alkaline phosphatase, but not of lactate dehydrogenase
Slightly to moderately elevated level of serum interleukin-6
Negative autoantibodies of definite autoimmune diseases
Histological findings
Increased megakaryocytes and reticulin fibrosis of the bone marrow
Exclusion of malignant lymphoma

which is not compatible with any known disease entity, so we call it TAFRO syndrome tentatively.

The differential diagnosis of TAFRO syndrome includes malignant lymphoma, especially angioimmunoblastic T-cell lymphoma,[2,3] lymphoma-associated hemophagocytic syndrome,[4] autoimmune diseases such as systemic lupus erythematosus, MCD and POEMS syndrome.

Histological examination of the bone marrow, liver (Cases 1, 2 & 4), spleen (Cases 2 & 4) and lymph node (Case 3) showed neither lymphoma cells nor hemophagocytic histiocytes, so malignant lymphoma was ruled out.

Although ANA was positive in two patients, diagnostically important autoantibodies for definite autoimmune diseases were all negative. Severe thrombocytopenia, elevated level of PA-IgG and megakaryocyte hyperplasia are common features of ITP, but myelofibrosis and systemic symptoms such as fever or anasarca are not usually presented in ITP.

Kojima *et al*. indicated that idiopathic MCD in Japan consists of two variants with distinct clinicopathological findings, that is, idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL)[5] type and non-IPL type.[6] IPL-type MCD resembles the plasma cell-type MCD in Western countries characterized by prominent polyclonal hyperimmunoglobulinemia, systemic manifestations such as malaise, fever and weight loss, and a high level of serum interleukin (IL)-6.[7,8]

Non-IPL-type MCD is characterized by mixed-type or HV-type Castleman's disease histology, a high incidence of pleural effusion and ascites, and is frequently associated with autoimmune disease during the course of the disease. Therefore, it was described that a portion of non-IPL-type cases may be secondary MCD, that is, autoimmune disease-associated LPD.[6]

MCD is a rare and enigmatic LPD characterized by a predominantly lymphadenopathic disease, and histopathologic features are essential for definitive diagnosis.[9] On the other hand, because lymphadenopathy of TAFRO syndrome was subtle or unrecognized, lymph node biopsy could be carried out in only one case, which showed HV-type Castleman's disease histology. Four patients with TAFRO syndrome demonstrated a slightly to moderately elevated serum IL-6 level (range : 7.2-64.9 pg/mL, normal < 4.0 pg/mL). A portion of TAFRO syndrome cases may be included in non-IPL-type MCD with pleural effusion, ascites and thrombocytopenia, but most cases of TAFRO syndrome can be distinguished from MCD due to an absence of obvious lymphadenopathy.

POEMS syndrome is a paraneoplastic syndrome due to an underlying plasma cell neoplasm.[10,11] The two major mandatory criteria for the syndrome are polyradiculoneuropathy and clonal plasma cell disorder, and the other major criteria include sclerotic bone lesions, elevated vascular endothelial growth factor and the presence of Castleman's disease. Minor features include organomegaly, endocrinopathy, characteristic skin changes and extravascular volume overload, that is, pleural effusion, ascites and edema. Between 11 and 30% of POEMS patients who have a documented clonal plasma cell disorder also have documented Castleman's disease or Castleman-like histology.[11]

Although TAFRO syndrome shows some of the minor features of POEMS syndrome, patients with TAFRO show neither polyradiculoneuropathy nor clonal plasma cell disorder. The serum vascular endothelial growth factor level of TAFRO syndrome was normal or slightly elevated (range : 31-285 pg/mL, normal < 115 pg/mL).

Bone marrow aspiration was unsuccessful in most patients with TAFRO syndrome, and biopsy specimens revealed increased megakaryocytes and reticulin fibrosis in all patients. Myelofibrosis is rarely associated with autoimmune diseases especially systemic lupus erythematosus.[12] The response to steroid therapy in most patients with autoimmune myelofibrosis suggests the background of systemic immunological abnormality.[13]

Semi-pulse therapy with methyl-PSL was started in three patients with TAFRO syndrome but was unsuccessful, and two patients needed hemodialysis and the other needed respiratory support. Although high-dose (1 mg/kg) and long-term PSL therapy may be effective, the adverse effects of PSL are problematic and tapering of PSL to an allowable maintenance dose is difficult due to relapse. Immunosuppressive therapy with CsA in combination with PSL was effective in two out of three patients, and the pulse therapy with cyclophosphamide was more useful in the other patient. Finally, one out of five patients with TAFRO syndrome died of multiple organ failure, in spite of vigorous immunosuppressive and supportive therapy. Autopsy findings revealed disseminated CMV infection and marked hemophagocytic syndrome, but neither malignant lymphoma nor other specific findings.

As described above, TAFRO syndrome (tentative term) is not compatible with any known disease entity, and we had

serious diagnostic and therapeutic problems. We suggest that this is a systemic inflammatory disease with a background of immunological abnormality, and vigorous immunosuppressive therapy should be started as soon as this peculiar disease is recognized.

By the accumulation of case studies, we hope to clarify the diagnostic importance of histological features of lymph node, the significance of bone marrow fibrosis, and the relationship between TAFRO syndrome and non-IPL-type MCD or other related diseases. Finally, it is hoped that these studies will define the clinicopathological aspects involved in the diagnosis and pathogenesis of TAFRO syndrome, and lead to appropriate therapy for this disease.

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