

[ ORIGINAL ARTICLE ]

## Subclinical Hypothyroidism in TAFRO Syndrome

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### Abstract:

**Objective** TAFRO syndrome is rare, and its underlying mechanisms currently remain unknown. Furthermore, standard therapeutic strategies have yet to be established. One of the hallmarks of TAFRO is pathological hypercytokinemia, which involves vascular endothelial growth factor (VEGF). A correlation has been reported between elevated VEGF and TSH levels in patients with hypothyroidism. Although hypothyroidism is a common endocrine abnormality, its clinical significance in TAFRO syndrome remains unclear.

**Methods and Patients** We investigated six patients diagnosed with TAFRO syndrome and examined their thyroid function in detail to obtain a deeper understanding of its relationship with cytokines and the manifestations of thyroid abnormalities as well as their clinical significance in TAFRO syndrome.

**Results** Five patients had subclinical hypothyroidism, while one had clinical hypothyroidism. Plasma VEGF levels were elevated in all patients, with a mean level of 256 pg/mL. Treatment with thyroxine supplements and immunotherapy or chemotherapy improved the symptoms of TAFRO syndrome without recurrence as well as increased the VEGF levels in three patients.

**Conclusion** The present results suggest that subclinical hypothyroidism may be a potential factor in the pathogenesis and symptomatology of TAFRO syndrome with VEGF elevation.

**Key words:** TAFRO syndrome, subclinical hypothyroidism, vascular endothelial growth factor (VEGF), thyroid function

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### Introduction

TAFRO syndrome is a subset of idiopathic multicentric Castleman disease (iMCD) that is characterized by thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, organomegaly, and typically normal immunoglobulin levels (1). Although its onset may be acute or subacute, its etiology remains unknown. Patients with TAFRO syndrome exhibit systemic inflammation, polyclonal lymphoproliferation, and a wide spectrum of symptoms caused by a cytokine storm that often includes interleukin (IL)-6 and vascular endothelial growth factor (VEGF) (2).

VEGF is an angiogenic and mitogenic substance that appears to be active in vascular endothelial cells and plays an important role in tumor growth and the metastatic process (3). It is also a vascular permeability factor that induces rapid and reversible increases in vascular permeability (3).

Relationships have been demonstrated between elevated VEGF levels and many pathological conditions (4-6), and a correlation has also been reported between elevated VEGF and TSH levels in patients with hypothyroidism (4). Although hypothyroidism is a common endocrine abnormality, its clinical significance in TAFRO syndrome remains unclear.

We investigated the thyroid function in detail to obtain a deeper understanding of its relationship with cytokines and the manifestations of thyroid abnormalities as well as their clinical significance in TAFRO syndrome. The present results indicate that even biochemical subclinical hypothyroidism causes severe clinical manifestations.

### Materials and Methods

Between January 2010 and January 2018, 6 patients (4 men and 2 women) were diagnosed with TAFRO syndrome

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**Table 1. Laboratory Results on Admission.**

Patient case No.	Sex	Age	WBC ( $\times 10^9/L$ ) (4-7)	Hb (mg/dL) (12-16)	Plt ( $\times 10^9/L$ ) (15-40)	CRP (mg/dL) (<0.3)	Cre (mg/dL) (0.4-0.8)	ALP (IU/L) (104-338)	IgG (mg/dL) (870-1,700)	sIL2R (U/mL) (145-519)
1	M	84	9.4	8.1	2.7	15	2.01	432	1,020	986
2	M	66	7.2	8.3	1.1	14.65	6.55	611	1,603	1,720
3	M	79	6.6	7.9	3.2	10.2	3.82	630	1,016	1,150
4	F	72	14.3	9.6	3.4	7.45	2.32	480	1,200	1,630
5	F	67	21.3	7.4	2.3	25.5	3.46	650	1,120	1,100
6	M	78	11.7	9.6	1.8	32.7	2.13	526	1,280	1,849

WBC: white blood cells, Hb: hemoglobin, Plt: platelets, CRP: C-reactive protein, ALP: alkaline phosphatase, IgG: immunoglobulin G, sIL2R: soluble interleukin-2 receptor

**Table 2. Results of Auto-antibody, CT Findings, Lymph Node Biopsy Findings, and Bone Marrow Aspirate and Trephine Biopsy Findings on Admission.**

Patient case No.	Auto-antibody	CT findings	Lymph node biopsy findings	Bone marrow aspirate and biopsy findings
1	HLA-Ab	ascites, splenomegaly	ND	myelofibrosis, increased level of megakaryocytes
2	HLA-Ab, ss-A, ss-B	pleural effusion, ascites, splenomegaly	hyaline-vascular type	myelofibrosis, increased level of megakaryocytes
3	HLA-Ab	pleural effusion, ascites, splenomegaly	mixed type	myelofibrosis
4	HLA-Ab	pleural effusion, ascites, splenomegaly	hyaline-vascular type	myelofibrosis, increased level of megakaryocytes
5	ss-A, ss-B	pleural effusion, ascites, splenomegaly	hyaline-vascular type	increased level of megakaryocytes
6	ss-A, ss-B, HLA-Ab	pleural effusion, ascites, splenomegaly	ND	increased level of megakaryocytes

CT: computed tomography, HLA-Ab: human leukocyte antigen-antibody, ND: not done

in our hospital. All patients presented with anasarca (pleural effusion and ascites), thrombocytopenia, anemia, renal dysfunction, ALP elevations, or low LDH levels. Other clinical findings included myelofibrosis, increased levels of megakaryocytes in bone marrow, and small or unclear lymphadenopathy on computed tomography (CT). All patients met the diagnostic criteria for TAFRO syndrome (6). Patient details are given in Tables 1 and 2.

The thyroid function was assessed in all patients. We evaluated the levels of thyroid-stimulating hormone (TSH) (normal range: 0.43-4.82  $\mu$ IU/mL), free T3 (FT3) (normal range: 2.39-3.86 pg/mL), free T4 (FT4) (normal range: 0.87-1.72 ng/dL), antithyroid peroxidase antibody (TPO Ab) (normal range: <9.4 IU/mL), and antithyroglobulin antibody levels (TG Ab) (normal range: <54.6 IU/mL). The thyroid function was classified as euthyroidism (normal TSH and FT4 levels), subclinical hypothyroidism (elevated serum TSH levels in association with normal serum FT4 levels), and clinical hypothyroidism (a reduction in FT4 with increased serum TSH levels).

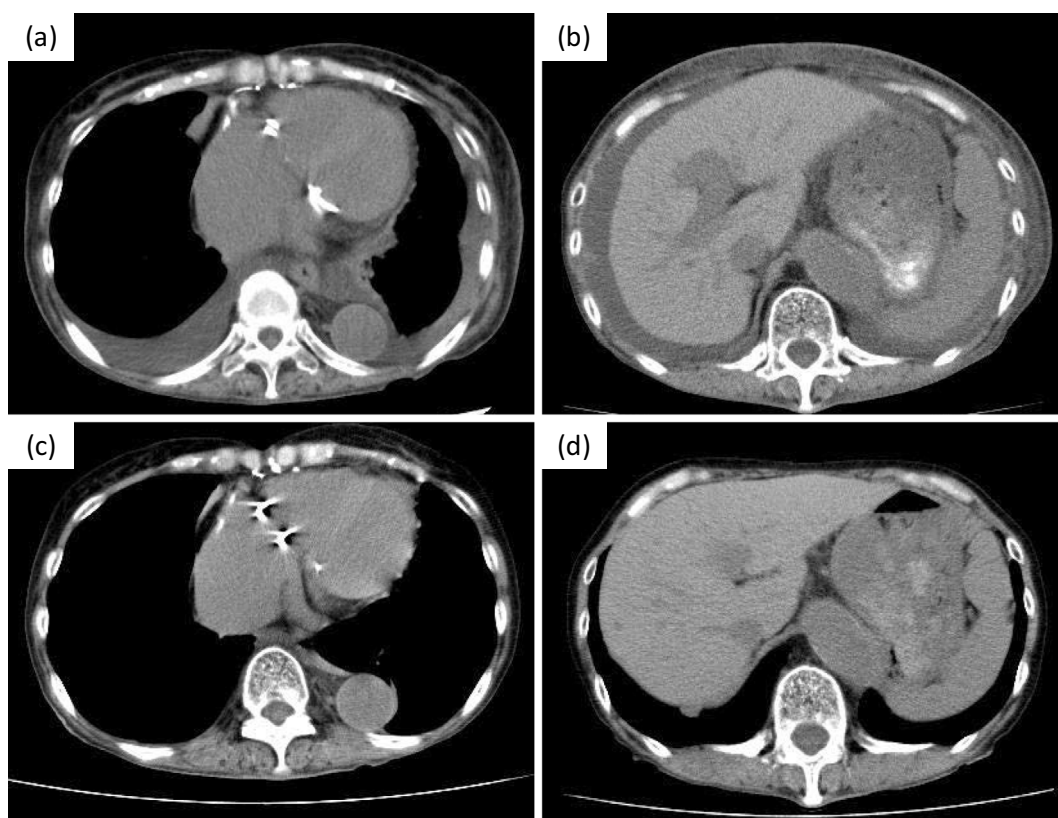
Plasma VEGF (normal range: <38.3 pg/mL) and serum IL-6 (normal range: <4.0 pg/mL) levels were measured by an enzyme-linked immunosorbent assay.

All patients provided their written informed consent to receive each regimen, and treatment was administered accord-

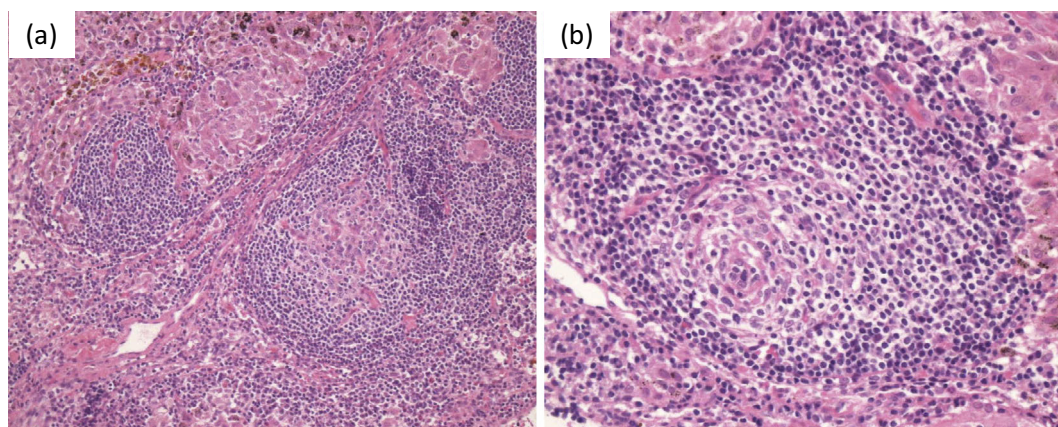
ing to the principles of the Declaration of Helsinki. This study was approved by the institutional ethics committee.

## Results

All patients had moderate to severe thrombocytopenia, anemia, and elevated CRP and ALP values (Table 1). All patients had peripheral edema, ascites, pleural effusion, and pericardial effusion. Four patients had peripheral edema as the initial and dominant symptom. All patients had hypoproteinemia. All patients were negative for HHV8, HIV, and Epstein Barr virus. Serum rheumatoid factor and antibodies, including antinuclear, anti-DNA, anti-Sm, anti-RNP antibodies, the perinuclear anti-neutrophil cytoplasmic antibody, and cytoplasmic anti-neutrophil cytoplasmic antibody, were all negative. Three patients (cases 2, 5, and 6) had anti-SS-A and anti-SS-B bodies but no symptoms of Sjögren's syndrome. In five patients (cases 1, 2, 3, 4, and 6), the anti-HLA class I antibody was positive. Four patients (cases 1, 2, 3 and 4) had diabetes. CT findings revealed small lymphadenopathy (<2 cm in diameter), bilateral pleural effusion, ascites, or splenomegaly (Table 2, Fig. 1a and b). The lymph node biopsy specimens of four patients (cases 2-5) showed atrophic germinal centers, an expanded interfollicular zone, the proliferation of highly dense endothelial venules, and



**Figure 1.** Computed tomography (CT) on admission and after treatment with thyroxine supplements. (a, b) CT showing bilateral pleural effusion, ascites and splenomegaly. (c, d) CT showing the disappearance of bilateral pleural effusion and ascites.



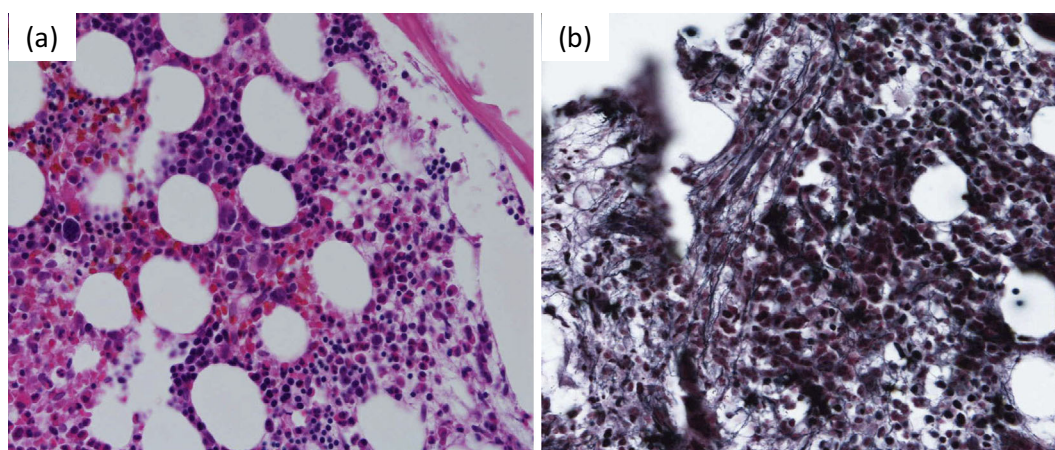
**Figure 2.** Histological findings of TAFRO syndrome lymph nodes (a, b). (a) A biopsy specimen of a mildly enlarged lymph node showing atrophic centers and intact sinuses (Hematoxylin and Eosin staining,  $\times 20$ ). (b) The marked proliferation of high endothelial venules was observed in germinal centers and interfollicular zones ( $\times 40$ ).

few plasma cells (Table 1, Fig. 2). Bone marrow aspiration and a biopsy were performed on all patients and revealed hypercellular marrow with myelofibrosis or an increased number of megakaryocytes without pathological cells or the dysplastic changes of hemophagocytosis (Table 2, Fig. 3).

The results of the thyroid function study as well as levels of auto-antibodies, serum IL-6, and VEGF are summarized in Table 3. Antithyroid peroxidase antibodies and antithy-

roglobulin antibodies were positive in all cases. Five patients (cases 1-4, 6) had subclinical hypothyroidism, while one (case 5) had clinical hypothyroidism. Common symptoms in these six patients included tiredness, lethargy, and weight gain.

Plasma VEGF levels were elevated in all cases, with a mean level of 256 pg/mL. Serum IL-6 levels were elevated slightly, with a mean level of 14.8 pg/mL (Table 3).



**Figure 3.** Histological findings of TAFRO syndrome bone marrow (a, b). (a) A biopsy specimen showing hypercellular marrow ( $\times 20$ ). (b) Silver staining showing a very loose network of reticulin fibers ( $\times 20$ ).

**Table 3.** Results of Thyroid Function Study and Serum IL-6 and Plasma VEGF Levels on Admission.

Patient case No.	TSH ( $\mu\text{IU/mL}$ ) (0.43-4.82)	FT4 (ng/dL) (0.87-1.72)	FT3 (pg/dL) (2.39-3.86)	TPOAb (IU/mL) ( $<9.4$ )	TGAb (IU/mL) ( $<54.6$ )	IL-6 (pg/mL) ( $<4$ )	VEGF (pg/mL) ( $<38.3$ )	Symptoms
1	6.23	0.9	2.42	23.4	87	10.2	230	tiredness, weight gain
2	9.46	0.87	2.2	76.4	260	12.3	323	tiredness, weight gain
3	6.01	1.24	2.1	19.6	230	24	224	tiredness, lethargy, weight gain
4	8.82	1.1	1.98	56	705	21.2	250	tiredness, weight gain
5	8.4	0.6	1.3	34	243	6.5	249	tiredness, weight gain
6	9.3	0.93	0.4	42	112	6.3	262	tiredness, weight gain

TSH: thyroid stimulatingthyroid-stimulating hormone, FT4: free T4, FT3: free T3, TPOAb: antithyroid peroxidase antibody, TGAb: antithyroglobulin antibody, IL-6: interleukin-6, VEGF: vascular endothelial growth factor

**Table 4.** Treatments and Outcomes of Patients.

Patient case No.	Treatment	Thyroxine supplement	Laboratory data after the treatment									Outcome
			WBC ( $\times 10^9/\text{L}$ )	Hb (mg/dL)	Plt ( $\times 10^9/\text{L}$ )	CRP (mg/dL)	Cre (mg/dL)	ALP (IU/L)	TSH ( $\mu\text{IU/mL}$ )	FT4 (ng/dL)	VEGF (pg/mL)	
1	mPSL, PSL	ND	7.5	10.2	6.3	0.3	0.76	230	7.23	0.86	240	died at 20 months due to relapse
2	mPSL, PSL	ND	5.6	9	4.2	1.4	2.45	520	10.4	0.76	280	died at 3 months due to sepsis
3	mPSL, rituximab	ND	3.8	9.4	8.4	0.62	1.32	420	8.6	0.88	226	died at 40 months due to relapse
4	mPSL, CyA, R-CHOP, toralizumab	100 $\mu\text{g/day}$	6.5	11.2	15.3	0.31	0.89	246	2.79	1.02	10.2	improved and alive at 46 months
5	mPSL, CyA	150 $\mu\text{g/day}$	3.4	10.6	14.2	0.42	1.1	302	2.79	1.6	22	improved and alive at 10 months
6	mPSL, CHOP	150 $\mu\text{g/day}$	3.2	10.3	8.7	1.3	1.3	335	1.63	0.93	16	improved and alive at 4 months

WBC: white blood cells, Hb: hemoglobin, Plt: platelets, CRP: C-reactive protein, Cre: creatinine, ALP: alkaline phosphatase, TSH: thyroid stimulatingthyroid-stimulating hormone, FT4: free T4, VEGF: vascular endothelial growth factor, mPSL: methylprednisolone, PSL: prednisolone, CyA: ciclosporin, ND: not done

As shown in Table 4, All patients were treated with glucocorticoids. In cases 1 and 3, thrombocytopenia and renal dysfunction improved, whereas peripheral edema, ascites, and pleural effusion remained and relapsed with VEGF and TSH elevation. Case 2 died of sepsis three months after the disease onset. Three patients (cases 4, 5, and 6) received thyroxine supplement treatment. A dose of 100-150  $\mu\text{g/day}$  was effective in these patients. Following the administration

of thyroxine supplements at the same time as combination immunotherapy or chemotherapy, edema, effusion, thrombocytopenia, the results of renal and thyroid function tests and plasma VEGF levels improved (Table 4, Fig. 1c and d). The condition of these three patients has since remained stable with no further evidence of TAFRO syndrome.

## Discussion

This study extends our previous study of TAFRO syndrome (7). To our knowledge, this is the first study that demonstrates the relationship between subclinical hypothyroidism and TAFRO syndrome with VEGF elevation.

VEGF induces a rapid and reversible increase in vascular permeability, which may induce the development of clinical manifestations, such as ascites, pleural effusion, peripheral edema, and organomegaly. A relationship between edema and increased VEGF levels was recently reported for POEMS syndrome, which often accompanies an extravascular volume overload (4, 5). VEGF is expressed in a number of normal adult tissues, including the kidneys, lungs, uterus, ovary, brain, heart, skin, pituitary gland, and macrophages. It has been demonstrated *in vitro* that VEGF is produced by thyroid follicular epithelial cells in response to the stimulation of the TSH receptor (8). Secreted VEGF was shown to stimulate VEGF receptors on the endothelial cells of thiouracil-fed rats via a TSH-dependent paracrine mechanism, leading to the proliferation of endothelial cells and hypervascularity of the thyroid gland. Klein et al. reported that recombinant human TSH stimulation for three weeks induced local VEGF expression in normal human thyroid grafted into nude mice (9). Iitaka et al. showed that serum VEGF levels positively correlated with TSH levels in patients with Hashimoto's thyroiditis (10). Furthermore, Sorvillo et al. suggested that TSH *in vivo* may regulate the VEGF production from extrathyroidal tissues (11). One possible explanation for this is that VEGF levels may be increased by the prolonged stimulation of TSH. Secreted VEGF may then stimulate VEGF receptors on endothelial cells, leading to an increase in vascular permeability and the development of TAFRO syndrome. In general, previous reports have suggested that levothyroxine treatment is unlikely to reduce symptoms in people with modest elevations in TSH levels and minimal symptoms at baseline, but such a treatment may have benefit in symptomatic patients, particularly in those who have high TSH levels (12-14). However, levothyroxine treatment may be beneficial for subclinical hypothyroidism with modest elevations in TSH levels in TAFRO syndrome, such as in the present cases.

In Castleman disease, hypothyroidism is the most common endocrine manifestation, being observed in 58% patients (15). Yu et al. reported that 39% of iMCD patients had a history of autoimmune diseases, which were typically stable at the time of the diagnosis (16). Furthermore, they showed that treatments resulted in the improvement or resolution of both iMCD and the signs and symptoms of auto-

immune connective tissue diseases. Based on the overlap between iMCD and autoimmune diseases, autoimmunity may be responsible for initiating or perpetuating the cytokine storm in iMCD via an autoantibody antigenic stimulation. There is only one report describing the clinical significance of hypothyroidism in TAFRO syndrome (7), and subclinical hypothyroidism with the presence of autoantibodies suggests that autoimmunity is a pathological cause of TAFRO syndrome.

Although the clinical significance of hypothyroidism in TAFRO syndrome is unknown, VEGF levels decreased with improvements in the condition of three refractory cases after thyroid hormone replacement therapy in the present study. A possible explanation for this is that VEGF levels may be increased by the prolonged stimulation of TSH. Secreted VEGF may then stimulate VEGF receptors on endothelial cells, leading to an increase in vascular permeability and the development of TAFRO syndrome. Subclinical hypothyroidism may be one of the causes, although confirming this will require further investigations.

Various treatments (corticosteroids, cyclosporin, rituximab, cytotoxic lymphoma-based chemotherapies, tocilizumab, siltuximab, bortezomib, thalidomide, and anakinra) have been used for patients with iMCD (5, 17, 18); however, relapse is common, and standard protocols have not yet been established (1). The pathogenesis of iMCD and TAFRO syndrome need to be elucidated in more detail in order to provide additional candidate targeted therapies.

The underlying mechanisms of and standard therapeutic strategies for TAFRO syndrome have yet to be established. Our results indicate that even biochemical subclinical hypothyroidism causes severe clinical manifestations, which prompted us to speculate that elevated VEGF levels are a potential factor in the pathogenesis and symptomatology of TAFRO syndrome with subclinical hypothyroidism. Further studies are needed to clarify its prognosis, pathophysiology, and appropriate treatments.

**The authors state that they have no Conflict of Interest (COI).**

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