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(CASE REPORT)

Peripheral hypothyroidism and TAFRO syndrome: Particularity of management

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Abstract

TAFRO syndrome is defined by the presence of thrombocytopenia, hydrops, fever, fibrosis, renal dysfunction, and organomegaly and can be seen with idiopathic multicentric Castleman disease (iMCD) or as an isolated process without iMCD. The pathophysiology of TAFRO is not well understood, but it is thought to be related to hypercytokinemia. Subclinical hypothyroidism may be a potential factor in the pathogenesis and symptomatology of TAFRO syndrome with elevated vascular endothelial growth factor (VEGF).There are no clear guidelines for the treatment of TAFRO in the absence of a definitive diagnosis of iMCD, resulting in suboptimal management and high morbidity. We report a case of hypothyroidism revealed by TAFRO syndrome.

Keywords: Hypothyroidism; TAFRO syndrome; VEGF; Management

1. Introduction

Hypothyroidism is a common pathology estimated at 3.1% [1]. TAFRO syndrome is rare, first described in 2010 in Japan, diagnosed as a particular form of multicentric Castleman's disease without proliferation of herpes virus type 8: HHV8, including thrombocytopenia, anasarca, fever, myelofibrosis, renal failure, and organomegaly [2]. Its correlation with hypothyroidism has been reported between elevated levels of vascular endothelial growth factor (VEGF) and TSH in patients with hypothyroidism. Although hypothyroidism is a common endocrine abnormality, its clinical significance in TAFRO syndrome remains unclear [3]. We report the case of TAFRO syndrome revealing severe hypothyroidism.

2. Observation

A 52-year-old woman, followed for 4 years for primary myelofibrosis confirmed on an osteomedullary biopsy that showed an estimated richness of 4 with myelofibrosis and maturation disorder of the granulocytic lineage, admitted for corticosteroid bolus therapy. On examination, the patient reported significant asthenia, dyspnea, and anorexia. Clinical examination showed a slowed down patient, febrile at 38.7 °C, bradycardic at 50 beats/min, hypotensive at 100/50mmHg, dry skin, ascites of little abundance, a non-palpable thyroid. Anasarca appeared progressively. Biological examinations showed: microcytic hypochromic anemia at 8.9 g/dL, severe thrombocytopenia (17,000 /uL), creatinine level at 4.3 mg/L, proteinuria, CRP at 13.58 mg/L, hypoalbuminemia: 25g/L. A picture of peripheral hypothyroidism with TSH at 21 µIU/l and T4 L <4,4 pmol/l, T3: 1,6 pmol/l and anti-TPO antibodies were negative, the cervical ultrasound showed a thyroid atrophy at the left lobe. The Trans thoracic ultrasound showed an ejection fraction of 55%.

The diagnosis of TAFRO syndrome associated with hypothyroidism was retained. Treatment with l-thyroxine at a dose of 1.7 ug/kg/d was initiated with a favorable evolution after 1 month of treatment with regression of the myxedema

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picture. Corticosteroid therapy with bolus of methylprednisolone was initiated, then associated with rituximab once a month.

3. Discussion

The diagnosis of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin myelofibrosis or renal dysfunction, and organomegaly) remains challenging due to its rarity, pleomorphic clinical presentation, and lack of consensus diagnostic criteria [4]. Two associations of diagnostic criteria were proposed in 2016. The first considered histology as necessary for diagnosis [5]. The second ones were recently updated [6,7] that required alĺ of the three major criteria (anasarca, thrombocytopenia, and fever or increased serum CRP level), two minor criteria among four (histological features of MCMI, myelofibrosis, and increased marrow megakaryocytes, organomegaly, and progressive renal failure). The diagnosis can be retained in our study which we report, since it fulfills all these criteria apart from the histological minor criterion. The particularity of this case is the association with severe hypothyroidism. We report the case of a middle-aged woman diagnosed with TAFRO syndrome associated with severe hypothyroidism.

Satoko Oka et al reports that subclinical hypothyroidism may be a potential factor in the pathogenesis and symptomatology of TAFRO syndrome with elevated vascular endothelial growth factor (VEGF) [3]. To our knowledge, this is the first study to demonstrate the relationship between subclinical hypothyroidism and TAFRO syndrome with VEGF elevation.

VEGF induces a rapid and reversible increase in vascular permeability, which can induce the development of clinical manifestations, such as ascites, pleural effusion, peripheral edema and organomegaly. VEGF is expressed in a number of normal adult tissues, including kidney, lung, uterus, ovary, brain, heart, skin, pituitary, and macrophages. VEGF has been shown in vitro to be produced by thyroid follicular epithelial cells in response to TSH receptor stimulation [8]. Previous studies have reported that levothyroxine treatment is unlikely to reduce symptoms in individuals with modest elevations in TSH levels and minimal symptoms at baseline, but that such treatment may be beneficial in symptomatic patients, particularly those with elevated TSH levels [9]. However, levothyroxine treatment may be beneficial for subclinical hypothyroidism with modest elevations in TSH levels in TAFRO syndrome, as in our present case. Only one report describes the clinical significance of hypothyroidism in TAFRO syndrome [10], and subclinical hypothyroidism with the presence of autoantibodies suggests that autoimmunity is a pathologic cause of TAFRO syndrome. Although the clinical significance of hypothyroidism in TAFRO syndrome is unknown, it is reported by Satoko Oka et al that VEGF levels decreased with improvement in three refractory cases after thyroid hormone replacement therapy [3]. A possible explanation for this phenomenon is that VEGF levels may be increased by prolonged TSH stimulation. The secreted VEGF may then stimulate VEGF receptors on endothelial cells, leading to increased vascular permeability and the development of TAFRO syndrome. Subclinical hypothyroidism could be one of the causes, although confirmation of this hypothesis requires further investigation. The underlying mechanisms and standard therapeutic strategies for TAFRO syndrome have not yet been established. Given the pathophysiology of this disease, characterized by a cytokine storm with increased VEGF levels and a possible autoimmune phenomenon (partly explaining the hypothyroidism and thrombocytopenia) [11;12] different treatments have been used. No study shows which treatment is best. Corticosteroids are the most commonly used first-line treatment in patients with TAFRO, but they are effective in only about 50% of cases.

4. Conclusion

The clinical significance of hypothyroidism in TAFRO syndrome and subclinical hypothyroidism with the presence of autoantibodies suggests that autoimmunity is a pathological cause of TAFRO syndrome. The course is favorable after initiation of replacement therapy.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interests.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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