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CLINICAL CASE

Development of nephrotic syndrome in a patient with Hashimoto's Thyroiditis

Desarrollo de Síndrome nefrótico en paciente con Tiroiditis de Hashimoto

Gianfranco Tomarelli R.[a], Camila Ampuero A.[a], Pilar Hevia J.[b], Alejandro Donoso F.[a], Daniela Arriagada S.[a]

[a]Unidad de Paciente Crítico Pediátrico. Hospital Clínico Dra. Eloísa Díaz I. La Florida. Santiago. Chile.
[b]Hospital San Juan de Dios. Santiago. Chile.

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What do we know about the subject matter of this study?

In 10% to 30% of cases of autoimmune thyroiditis, proteinuria appears as a manifestation of secondary renal involvement.

What does this study contribute to what is already known?

To report and recall the existence of this complication, reviewing the different pathophysiological mechanisms involved.

Abstract

The development of nephrotic syndrome in concomitance with Hashimoto's thyroiditis is an infrequent association in the pediatric age. **Objective:** To report an infrequent complication of autoimmune thyroiditis, such as the appearance of nephrotic syndrome. **Clinical Case**: A 10-year-old patient presenting with nephrotic syndrome and goiter. A history of autoimmune thyroiditis and untreated hypothyroidism was detected. Corticosteroid and hormone replacement therapy (levothyroxine) is started, achieving a good clinical and laboratory response. **Conclusion:** Autoimmune thyroiditis impacts renal physiology through immunological and non-immunological mechanisms. At the same time, renal repercussions can affect thyroid function. The importance of this communication lies in reporting an infrequent complication of autoimmune thyroiditis, such as the appearance of nephrotic syndrome.

Keywords:
Nephrotic Syndrome;
Hypothyroidism;
Thyroiditis;
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Correspondence:
Gianfranco Tomarelli Rubio
gtomarelli@uc.cl

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Introduction

Hashimoto's thyroiditis is an infrequent chronic autoimmune pathology in childhood, usually presenting during adolescence[1]. The most frequently described complications are the development of hypothyroidism, hypovitaminosis D2 and, occasionally, thyroid storm[3]. Likewise, there is evidence of association with other autoimmune diseases[4] such as autoimmune pancreatitis, Sjögren's syndrome[5], and steroid-responsive encephalopathy[6].

Hypothyroidism affects renal physiology, either directly[7] or indirectly, through its action on systemic and local hemodynamics[8,9]. Renal involvement with proteinuria in autoimmune thyroiditis is not infrequent, occurring in 10-30% of cases, and improves by treating the thyroid pathology, however, associated glomerulopathy is not a frequent finding. In pediatric patients, the coexistence of autoimmune thyroid pathology with nephrotic syndrome (NS) has been rarely reported[10].

We report the case of a 10-year-old girl with autoimmune Hashimoto's thyroiditis, without previous treatment, who presented NS, with good response to steroid therapy. The objective of this report is to describe the association between Hashimoto's thyroiditis and NS by briefly reviewing the possible pathophysiological mechanisms involved in the interaction between the kidney and the thyroid.

Clinical Case

We present the case of a 10-year-old female patient, with no family history of thyroid disease, who was diagnosed with goiter at 9 years of age (thyroid ultrasound findings compatible with chronic thyroiditis), with the presence of positive antithyroid antibodies, and not treated at the time of hospital admission. She presented to the Emergency department due to a 5-day history of foamy urine associated with abdominal pain, profuse vomiting, and diarrhea. The day before admission, she developed periorbital and peripheral edema, decreased urine output, weakness, and 38°C fever. At the time of evaluation, she presented bilateral periorbital and pretibial edema, with evident goiter (painless and without palpable nodules), and the presence of grade IV/VI systolic ejection murmur located in the pulmonary area without irradiation, with no other significant alterations in the rest of the physical examination. Her blood pressure was 120/78 mmHg (95th percentile), temperature 38.1°C, and her anthropometric measurements were as follows: weight 33.9 kg, height 131.5 cm (p7), and BMI 19.8 (p83).

Within the tests on admission highlighted complete urine test with proteinuria +++, no bacteria, no nitrites, leukocytes 7 cells/uL (NV: 0-10 cells/uL), erythrocytes 4 cells/uL (NV: 0-15 cells/uL), urine protein/creatinine ratio (P/C ratio) 2 mg/mg, total proteins 3.8 g/dL, hypoalbuminemia 2.1 g/dL, hypercholesterolemia 416 mg/dL, hypertriglyceridemia 127 mg/dL, and plasma creatinine 0.46 mg/dL (creatinine clearance calculated by Schwartz formula: 125 ml/min/1.73 m^2). Venous blood gases, plasma electrolytes, and hemogram were within normal ranges. The immunological study showed immunoglobulin A 181 mg/dL (NV: 45-236), immunoglobulin M 131 mg/dL (NV: 52-242), immunoglobulin G 208 mg/dL (NV: 608-1572), C3 125 mg/dL (NV: 80-150), and C4 37.3 mg/dL (NV: 12-36). The renal ultrasound was normal. The patient was admitted with a diagnosis of NS and autoimmune thyroiditis.

The NS was treated with prednisone (60 mg/m^2/day), with good response, achieving edema resolution, and progressive decrease of proteinuria until reaching normal ranges before discharge (discharge P/C ratio: 0.09, at 6 days).

Regarding the thyroid function study, it showed thyroid stimulating hormone (TSH) 4.4 IU/ml (NV: 0.67-4.16 IU/ml), free thyroxine (FT4) 0.80 ng/dL (NV: 0.86-1.4 ng/dL), anti-peroxidase antibodies (Anti Tpo) 120 U/ml (NV: 0-60 U/ml), and anti-thyroglobulin antibodies (Anti-Tg) 82 U/ml (NV: 0-60 U/ml), so substitution therapy with levothyroxine (25 mcg/day) was started. Thyroid ultrasound showed a normal-sized thyroid and a slight increase of diffuse vascularization in the Doppler ultrasound, without solid or cystic focal lesions, suggesting thyroiditis. The rest of the study (PCR for SARS CoV-2, anti-neutrophil cytoplasm antibodies, antinuclear antibodies, anti-DNA antibodies, anti-streptolysin O antibodies, anti-cardiolipin antibodies, anti-myeloperoxidase antibodies, and anti-proteinase 3 antibodies) was negative.

Six days after admission, the patient was in good condition and was discharged with prednisone (60 mg per day) and levothyroxine (25 µg per day). At 12 months of follow-up, the patient was asymptomatic and thyroid pathology was controlled (TSH 1.11 IU/ml) with substitution treatment. She has not presented NS relapses (urine test without proteinuria and serum creatinine 0.44 mg/dL).

Discussion

In the case described, although no histological study was performed, the corticosensitive behavior of NS could be suggestive of a minimal change type histology. In pediatric patients, the coexistence of primary hypothyroidism caused by autoimmune thyroiditis and NS due to minimal changes is rare but, in the adult

population, this association has been frequently reported, although the NS is usually caused by a systemic disease[11].

There are several systemic or organ-specific autoimmune diseases related to Hashimoto's thyroiditis such as sarcoidosis[12] and vitiligo[13], usually occurring in succession[14] and simultaneously.[10], although this is very uncommon. Very rarely, edema and proteinuria may also develop in relation to the thyrotoxic phase of autoimmune thyroiditis in the pediatric patient[15].

Among the glomerular histologic findings most frequently associated with autoimmune thyroid disease are membranous glomerulopathy, IgA nephropathy, and focal segmental glomerulosclerosis, while minimal change disease is much less frequent which may also be underestimated, considering that patients with corticosensitive nephrotic syndrome are not histologically studied[16,17,18].

Immune-mediated glomerular disease in Hashimoto's thyroiditis would be caused by immunological and non-immunological mechanisms (figure 1). Among the first ones, we found immune complex depositions formed by thyroglobulin and antithyroglobulin antibodies at the glomerular level[19], which is mainly described for membranous nephropathy, as well as by the direct action of antibodies against certain epitopes of glomerular and tubular antigens. One of these epitopes is megalin, a protein that is expressed in both thyrocytes and proximal tubule cells. The breakdown of immunological tolerance to this autoantigen, a mechanism described at the experimental level, could lead to an immune response against podocytes[20]. In addition, after an abnormal activation of B and T lymphocytes to thyroid antigens[21,22], the production of cytokines by Th2 lymphocytes is activated which can alter the glomerular filtration barrier through complex mechanisms[13,22].

Regarding the non-immunological mechanisms, they are caused by the effect of the decreased action of thyroid hormones at this level, which play a role in renal hemodynamics, affecting both glomerular function (glomerular filtration rate, GFR) and tubular function (sodium and water homeostasis)[23]. Hypothyroidism can affect GFR due to its negative inotropic action, causing a decrease in the secretion of atrial natriuretic peptide and erythropoietin[9]. In addition, by increasing peripheral vascular resistance due to the absence of the vasodilator effect of T3 on vascular smooth muscle

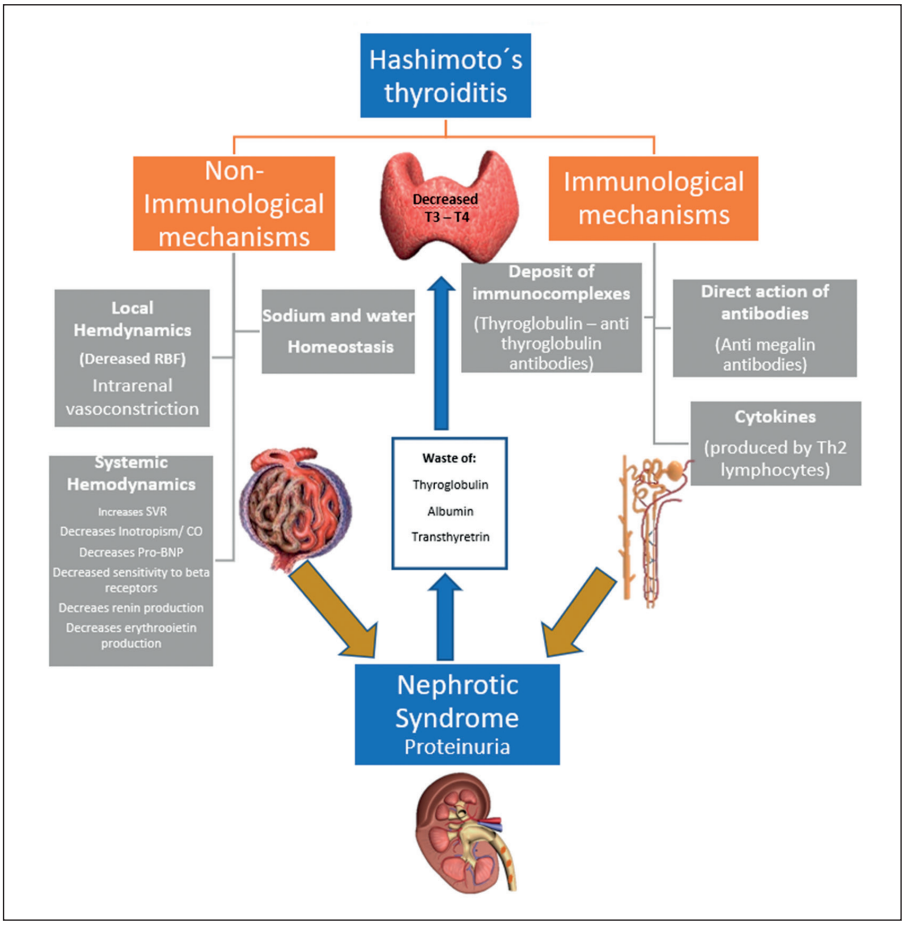

Figure 1. Diagram of the pathophysiological mechanisms involved in the interaction between kidney and Hashimoto's thyroiditis. RBF: Renal blood flow, SVR: Systemic vascular resistance, CO: Cardiac output, Pro-BNP: Atrial natriuretic peptide.

cells[24], renal blood flow and GFR decrease, activating the renin-angiotensin-aldosterone system, thus increasing tubular reabsorption of sodium and water.

On the other hand, T3 and free T4 levels regulate renin gene expression through the beta-adrenergic response. In addition, there is a decreased sensitivity to beta-adrenergic stimulation which could affect renin production[8,25].

As for tubular function, free thyroxine influences the expression of certain transporters and ion channels, such as the Na/K pump and Na/H and calcium transporters, which alters renal sodium and water handling, with development of hyponatremia due to decreased free water clearance, increased fractional excretion of sodium, and decreased renal concentrating capacity[20,26].

In patients with nephrotic syndrome, urine loss of the main transport proteins (thyroglobulin, transthyretin, and albumin) can trigger or exacerbate existing hypothyroidism, requiring an increase in the dose of levothyroxine which is necessary to decrease TSH levels[27]. It should be noted that in some patients euthyroidism may persist due to the compensatory increase in TSH.

Regarding treatment, there are reports of pediatric cases describing a decrease in antibody levels and normalization of thyroid hormones after administration of corticosteroid therapy for NS[10]. On the other hand, in adult patients with hypothyroidism and NS, it has been observed that levothyroxine supplementation increases plasma albumin, improves dyslipidemia, and decreases proteinuria[28]. However, no reliable association has been demonstrated between thyroid function and the magnitude of renal involvement and proteinuria, a finding that supports the autoimmune origin of this association.

In conclusion, the relationship between Hashimoto's thyroiditis and nephrotic syndrome is a complex association that involves immunological and non-immunological interactions between both parenchymas, making it necessary to evaluate thyroid function in the presence of renal pathology and vice versa. Considering the above, in patients with autoimmune thyroiditis who present persistent proteinuria, the existence of glomerulopathy should be ruled out, and, on the contrary, in all patients with glomerulopathy and persistent proteinuria, thyroid function should be evaluated independently of the therapy received.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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