CLINICAL CASE

NEWLY ONSET OF THYROTOXICOSIS IN A PATIENT TREATED WITH ANAKINRA FOR GLUCOCORTICOIDS-DEPENDENT AND COLCHICINE-RESISTANT RECURRENT PERICARDITIS

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ABSTRACT

Anakinra, a recombinant, but slightly modified version of the non-glycosylated form of human interleukin-1 receptor antagonist, has been used for various conditions, including the most recent indication, namely, some forms of sever coronavirus infection. Despite a large area of immune and autoimmune interferences and side effects, no specific endocrine issue has been highlighted yet. Here, we report a young female who was prior confirmed with a history of recurrent liquid pericarditis that turned out to be resistant to glucocorticoids and colchicine, thus Anakinra was initiated and showed good clinical results. However, the patient started to experience a mild, but suggestive, clinical picture of thyrotoxicosis which was confirmed by the lab findings. Despite negative thyroid antibodies, the subject did not undergo medication with anti-thyroid medication, only with beta-blockers, and showed a progressive clinical remission within a few weeks. Also, a correction of the thyroid function was observed followed by a spontaneous switch to primary hypothyroidism in addition to a mild elevation of the serum anti-thyroperoxidase antibodies, consistent with the diagnosis of an autoimmune thyroid disease. Whether prior glucocorticoids exposure had a negative impact of the level of antibodies against thyroid or Anakinra was responsible for de novo induction of these mentioned thyroid anomalies is yet to be proven. Moreover, it is still a matter of debate the role played by the positive family history with respect to the same autoimmune thyroid condition that might raise the issue of a selective group of Anakinra candidates that are prone to develop thyroid consequences. Further clinical and pathogenic studies are necessary on this particular novel insight.

KEYWORDS: *Anakinra, pericarditis, thyrotoxicosis, interleukin-1 receptor antagonist, autoimmune thyroid disease*

INTRODUCTION

Anakinra, a recombinant, but slightly modified version of the non-glycosylated form of human interleukin-1 receptor antagonist (IL-1 RA), blocks IL-1 activity by competitively inhibiting its ability to bind to the receptor. It has been produced by recombinant DNA technology using Escherichia coli bacterial expression system; however, it is different from the native human IL-1 RA by the addition of a methionine residue at its amino-terminus. Traditionally (despite being two decades since the official approval in US and Europe) it has been used for various conditions such as rheumatoid arthritis, neonatal-onset multisystem inflammatory disease (NOMID), Still' disease, as well as periodic fever syndromes (also, named familial Mediterranean fever, respectively, cryopyrin-associated periodic syndromes) [1-3].

The mechanism of action involves blocking IL-1 binding to its type 1 receptor, which is expressed in a multitude of organs in the human body. Thus, it blocks the action of IL-1α and IL-1β, preventing the cascade of sterile inflammation, IL-1 been known to have a broad range of immune, and inflammatory roles. Moreover, cartilage degradation in rheumatoid arthritis due to rapid loss of proteoglycans and accelerated bone resorption has been positively improved by the drug. The local synovial concentration of IL-1 exceeds the natural ability of IL-1 RA to counteract its destructive effect [4-6].

Since 2020, recent COVID-19 (coronavirus disease 2019) pandemic brought us in prime-time unexpected clinical entities with various medical and surgical backgrounds [7,8]. In addition, the clinical applications of this drug with concern to a certain subgroup of individuals going through coronavirus infection, particularly regarding a high inflammatory status, has been highlighted starting with the first publications in 2021. The standard care of these patients admitted with high-risk infection was considered to be the use of dexamethasone especially in relationship with pulmonary involvement (including acute respiratory failure) [9-11]. Alternatively, for people who required supplemental oxygen therapy having symptoms and signs of significant inflammatory response, tocilizumab, an IL-6 receptor inhibitor, was used, as well, adding new elements to the immune and inflammatory-related drugs amid infection [12-14]. But IL-1 pathway raised a particular interest; it was observed that a potent NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome activation in patients with critical forms might imply the potential use of medication targeting IL-1 loops. Hence, the role of using IL-1 RA in COVID-19 takes into account the blockade of IL-1/IL-6 axis that is associated with a cytokine storm related to coronavirus infection [15-17].

Generally, the safety profile involves the most serious adverse reactions in subjects taking IL-1 RA in the field of infectious diseases such as upper respiratory tract infections, gastroenteritis, influenza like illness, nasopharyngitis, sinuzitis, neutropenia (particularly when used in combination with TNF blocking agents), injection site reactions (that might be experienced up to a half of the patients), etc. [18-20].

To our aware, so far, no specific endocrine interferences were reported in relationship with the use of recombinant human IL-1 RA despite the fact the one individual might synchronously associate a multitude of immune and autoimmune conditions mostly in relationship with a common genetic background (which is less or more understood/obvious in one subject) and some of them may belong to the endocrine site or others might represent rheumatologic or cardiologic issues that make the patient a candidate for therapy with Anakinra [21]. We aim to introduce the case of a young adult who experienced transitory thyrotoxicosis while being treated with Ankinra for recurrent pericarditis with a long history of poor response to prior standard medication, and while not being known with a previous hormonal anomaly.

CASE PRESENTATION

This is an 18-year-old female who is known with delay in neuro-psychological development related to suffering at birth (unknown circumstances); she was admitted for an endocrine check-up due to unexplained palpitations, nervousness, agitation and limbs tremor since several weeks. She has been diagnosed with a recurrent liquid pericarditis that turned out to be resistant to glucocorticoids and

colchicine, hence requiring the initiation of Anakinra, with massive improvement that allowed a progressive cessation of glucocorticoids exposure. Her family medical history includes her father who suffers from autoimmune Hashimoto's chronic thyroiditis.

Currently, the main physical examination findings are: macrochephaly, strabismus, rare dentition, thoracic kyphosis, bison's neck, abdominal distribution of fat, wide pink stretch marks on the posterior chest, abdomen, lumbar and inner thighs, subxiphoid keloid scar after pericardiocentesis, hypertrichosis; a regular pulse of 125 beats per minute, and blood pressure of 130/100 mmHg and a normal body mass index (Figure 1).

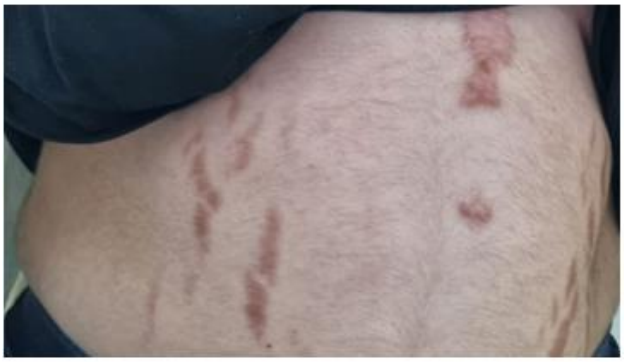

Figure 1 - This is an 18-year-old female with exogenous Cushing's syndrome due to prior glucocorticoids exposure for recurrent pericarditis; note the red abdominal stria, mild hirsutism, and keloid scar upon pericardiocentesis

A painless elastic goitre with regular surface and a fine tremor was noticed in both hands (apparently with recent onset). No thyroid eye disease (such as proptosis) was registered. The endocrine features were consistent with Cushing's syndrome (most probably an iatrogenic form due to prior medication for the cardiac condition) and a novel suspected diagnosis of thyrotoxicosis.

Further on, lab testing was performed. Blood assays confirmed thyrotoxicosis with negative anti-thyroid antibodies, namely: anti-thyroglobulin antibodies (TgAb), anti-thyroperoxidase antibodies (TPO), anti-TSH (Thyroid Stimulating Hormone) receptor antibodies (TRAb). Blood count and inflammatory markers were within normal limits. Hepatobiliary tests were mildly abnormal.

Thyroid ultrasound showed a normal sized gland with a homogeneous, mildly hypoechoic pattern and a normal vascularization according to the Doppler examination (Figure 2).

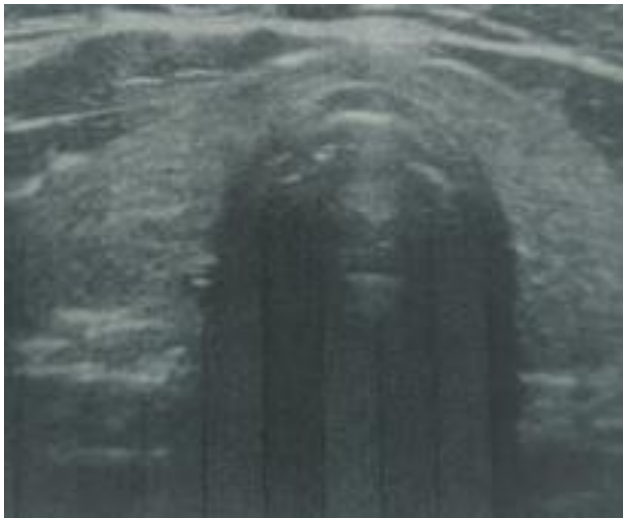

Figure 2 - Thyroid aspect via anterior neck ultrasound on first admission: homogenous pattern without nodules at transversal section (of note, normal Doppler exam makes less likely a hyperthyroidism)

Despite not having a positive thyroid autoimmunity, this was considered a flare-up (transitory) thyrotoxicosis and the patient was only treated with oral beta blockers (propranolol 40 mg/day depending on the pulse) and not with specific anti-thyroid medication. She was re-checked during the following months. The outcome was very good, with the clinical improvement in terms of pulse normalization, as well as nervousness and tremor remission within a few weeks.

Notably, after the first month of treatment, hepatobiliary tests normalized, thus suggesting a thyroid hormone anomalies-related pattern. During follow-up, a progressive increase of TSH and lowering of serum thyroid hormones was registered (as expected for this type of thyrotoxicosis). An adjustment of the propranolol dose (a lowering dose to 20 mg/day) was done. Two months after the propranolol reduction, primary hypothyroidism was confirmed while a mild increase of the TPO level was consistent with the diagnosis of autoimmune thyroid disease (as her father') (Table 1).

After 3 months since initial endocrine evaluation, thyroid ultrasound showed a stationary pattern (Figure 3). The patient remained under endocrine surveillance in addition to the complex multidisciplinary management of her prior conditions.

Parameter	On admission (start Propanolol)	After 1 month (reduction of Propanolol dose)	After another 2 months (indication to stop propranolol)	After another 2 months	Normal ranges	Units
TSH	0.006	0.025	**8.92**	**7.56**	0.51-4.3	µUI/ml
fT4	21.2	15.6	11.5	12.6	12.6-21	pmol/L
T3	3.6	2.1	1.6	NA	1.4-3.34	nmol/L
TRAb	<0.8	<0.8	NA	NA	1.75	UI/L
TPO	10	17	21	**34**	<26	UI/mL
TgAb	NA	15	13	NA	<64	UI/mL
Leukocytes	6.9	6.65	13.9	10.43	4-10	thousand/uL
Neutrophils	4.02	4.48	12.6	6.82	2-8	thousand/uL
Erythrocytes	4.51	5.1	5.17	5.27	3.8-5.1	thousand/uL
Thrombocytes	198	177	179	207	150-450	thousand/uL
ESR	9	6	NA	NA	<0	mm/1-hour
CRP	0.42	0.44	0.5	0.81	<5	mg/L
ALT	67	35	42	NA	<35	U/L
AST	54	28	31	NA	<35	U/L
GGT	50	31	35	NA	<40	U/L
Total bilirubin	0.45	0.37	0.42	NA	<1.2	mg/dL

Table 1 - Biochemistry panel of an 18-year-old female admitted for thyrotoxicosis; red stands for the diagnosis of thyrotoxicosis and associated liver effects; blue stands for switching to primary hypothyroidism; green shows a mild increase of TPO level that was suggestive enough for an autoimmune thyroid disease. ALT=aminotransferase; AST=alanine aminotransferase; GGT=gamma glutamyl transferase; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; TgAb=anti-thyroglobulin

DISCUSSION

This case highlights several important aspects of the clinical, but, also, pathogenic traits with respect to the diagnosed pathologies. Firstly, recombinant human IL-1 RA represents an elegant alternative for the glucocorticoid-resistant (or dependent), colchicine-resistant recurrent pericarditis and showed encouraging results in this case [22,23]. Despite not being a specific warning, thyroid profile proved abnormal and transitory thyrotoxicosis was developed; whether this represents an incidental finding remains a future topic to study. The profile of the antibodies against thyroid was negative; a potential impact of the prior glucocorticoids exposure might explain it (of note, the patient presented clinical features of exogenous Cushing's syndrome with a progressive remission upon corticosteroids medication was stopped) [24,25]. A supplementary tool to explore the flare-up mechanism of thyrotoxicosis should have been radioiodine uptake assessment which was not available in this instance. Alternatively, to the pitfalls of endocrine assays, we suggest a novel insight, whether Anakinra might induce an antibodies-negative thyroiditis as seen in other new drugs such as checkpoint inhibitors or mitotane, etc. [26-28].

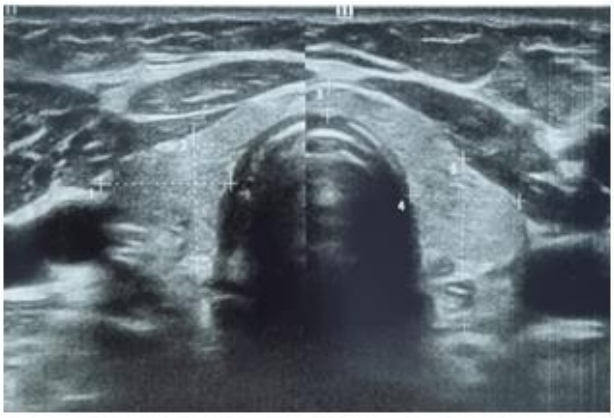

Figure 3 - Thyroid ultrasound after 3 months since initial diagnosis of the thyrotoxicosis: stationary

Additionally, most of the challenging cases that finally become Anakinra candidates should benefit from a genetic testing. Of note, an alternative differential diagnosis for this

recurrent pericarditis was COVID-19 infection itself amid pandemic days and even post-pandemic era [29,30]. In this case, the results of the pericentesis excluded this aetiology showing pericardial fluid with sterile exudate, without malignant, bacterial, fungal, viral or granulomatous elements. Since the autoimmune panel was not conclusive, genetic analysis was done and pinpointed a karyotype 46,XX while the whole exome sequence established that the patient is heterozygous for a 1.9 Mb deletion seq [GRCh37] del (5)(q35.2-35.30, chr5:g.175517250-177422999del, classified as pathogenic variant. In patients with recurrent pericarditis who respond to IL-1 RA, genetic studies play an important role in establishing the diagnosis of auto-inflammatory syndromes [31]. Similarly, in cryopyrin-associated periodic syndromes, a spontaneous mutation in CIAS1/NLRP3 gene who encodes cryopyrin was associated with hypersecretion of IL-1β which determines the systemic inflammatory component of the syndrome [32]. In patients with deficiency of IL-1 RA (DIRA) whose main clinical features are frequent episodes of systemic inflammation and associated inflammatory lesions affecting the bone, skin, joints, eyes or nervous system, there are underlying pathogenic variants of the IL1RN gene; this mentioned monogenic autosomal recessive disease being primary caused by the loss of IL-1 RA secretion [33].

Finally, transient excess of the thyroid hormones may be considered in the case of autoimmune thyroiditis (even with repeated negative autoantibodies), but, also, the differential diagnosis includes acute or subacute thyroiditis (in this case, we had repeated normal blood count and inflammatory markers), drug-induced thyroiditis (no history of IL-2, interferon alpha, lithium or amiodarone exposure was positive in this young female) or factitia tireotoxicosis. Overall, we should take into consideration the fact that IL-1 may regulate thyrocyte proliferation and local production of IL-1 by infiltrating monocytes thus contributing to the development of goitre in patients with autoimmune thyroid spectrum [34,35]. Further insights are mandatory to be studied with regard to Anakinra-related thyroid profile anomalies.

CONCLUSION

This case highlights a rare instance of a patient presenting with a transitory thyrotoxicosis developed while taking Anakinra treatment. We know that the IL-1 pathways could play a critical role in thyrocytes destruction amid hyperthyroidism/thyrotoxicosis, but therapy with IL-1 RA should counteract these effects. If there an “escape” mechanism or a particular subgroup of Anakinra candidates is already prone to a thyroid malfunction due to their underlying diseases and potential genetic background is still an open issue.

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