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CASE REPORT

Developing of granulomatous thyroiditis during etanercept therapy

Carlos A. Cañas · Gabriel J. Tobón · Luis G. Arango · Nora Guarín

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Abstract We describe a 32-year-old man who developed granulomatous thyroiditis (GT) during etanercept therapy for rheumatoid arthritis (RA). Fever and thyroid pain developed 8 months after administration of etanercept. Noncaseating epithelioid cell granulomas consistent with GT were detected in a thyroid biopsy. Tissue staining and cultures for bacteria, mycobacterium, and fungus were all negative. Etanercept therapy was withdrawn and steroids regime was indicated with clinical and laboratory improvement. A month after, the patient developed hypothyroidism and recurrence of RA. A year after, the patient is asymptomatic with rituximab, methotrexate, and levothyroxine therapy. We report a case of GT probably in an etanercept-induced granulomatous reaction context.

Keywords Etanercept · Granulomatous thyroiditis · Rheumatoid arthritis · Tumor necrosis factor-alpha

Introduction

Tumor necrosis factor-alpha (TNF-α) has been implicated in the pathogenesis of numerous inflammatory conditions, and its inhibition have proven efficacious in the treatment of autoimmune diseases such as rheumatoid arthritis (AR). Recent cases of granulomata reactions have been reported in anti-TNF-α therapy with etanercept, most notably sarcoidosis [1–5], sarcoidosis-like diseases [6–10], granulomatous hepatitis [11], and granulomatous dermatitis [12, 13]. Probably, we report the first case of granulomatous thyroiditis (GT) during etanercept therapy for a patient with RA.

C. A. Cañas (✉) · G. J. Tobón
Unit of Rheumatology, Fundación Valle del Lili,
Cra. 98 18-49 Cali, Colombia
e-mail: ccanas@telesat.com.co

L. G. Arango
Unit of Endocrinology, Fundación Valle del Lili,
Cali, Colombia

N. Guarín
Unit of Pathology, Fundación Valle del Lili,
Cali, Colombia

Case report

A 32-year-old man with a RA history was admitted with fever and thyroid pain of 3 days of evolution. Three years prior to admission, he had been treated with nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial drugs, methotrexate, and a steroid regime. After a flare up 8 months prior to his admission, he was placed on etanercept (25 mg twice a week). Before receiving etanercept, he was tested for hematological, liver, renal, and thyroid functions. Screening for latent or active tuberculosis were negative. These tests were within the normal range. Improvement was satisfactory, and steroids were withdrawn 8 weeks after etanercept onset. A week prior to admission, he developed progressive fatigue, malaise, anorexia, and fever in the afternoons. These symptoms were followed by progressive thyroid pain. The patient had no history of other autoimmune or thyroidal diseases. Upon physical examination, his temperature was 39.2°C, his blood pressure was 120/72 mmHg, and his pulse was 104 bpm. The palpation of thyroid was very painful and a diffuse increment of size was noted. Cardiopulmonary evaluation was normal. No painful or swelling joints were found. Laboratory tests showed

erythrocyte sedimentation rate was 90 mm/h, serum C-reactive protein concentration was 5.6 mg/dL, hemoglobin was 12.5 g/L, white cell count was 16.0 10^9/L with neutrophil count 12.8 10^9/L, and platelet count was 345 10^9/L. Ultrasound of the thyroid gland showed diffuse increase of size with altered echogenicity. Serum thyroid-stimulating hormone (TSH) was 0.0 mU/L, free thyroxine (fT4) hormone was high, and thyroid antibodies were negative. No other autoantibodies (antinuclear, anti-dsDNA, anticardiolipin, anti-extractable nuclear antigen) were present except a high titer of rheumatoid factor. A technetium-99m pertechnetate thyroid scintigraphic scan showed reduced uptake. Noncaseating epithelioid cell granulomas consistent with GT were detected in a thyroid biopsy (Fig. 1). Tissue staining and cultures for bacteria, mycobacterium, and fungus were all negative.

Etanercept was withdrawn and prednisolone 50 mg/day was indicated. His erythrocyte sedimentation rate, serum C-reactive protein concentration, neutrophil, and platelet counts normalized. Fever progressively decreased, and pain is not present in 4 days. A month after, the patient developed hypothyroidism and recurrence of RA. A year after, the patient is asymptomatic with rituximab, methotrexate, and levothyroxine therapy.

Discussion

This report describes the development of GT in a patient during etanercept therapy for RA. Immunological changes secondary to TNF-α inhibition, several reports of granulomatous diseases associated to use of etanercept, and temporal relationship were the criteria for considering this association. TNF-α plays a critical role in many aspects of immune system development, immune response regulation, and T cell-mediated tissue injury. TNF-α has both pro-inflammatory and immunoregulatory properties. TNF-α is a critical growth factor for thymocytes and plays an important role in the peripheral immune system in antigen-presenting cell function and in regulating apoptosis of potentially autoreactive T cells. Potential mechanisms for autoimmune development in the context of TNF-α inhibition are now being proposed.

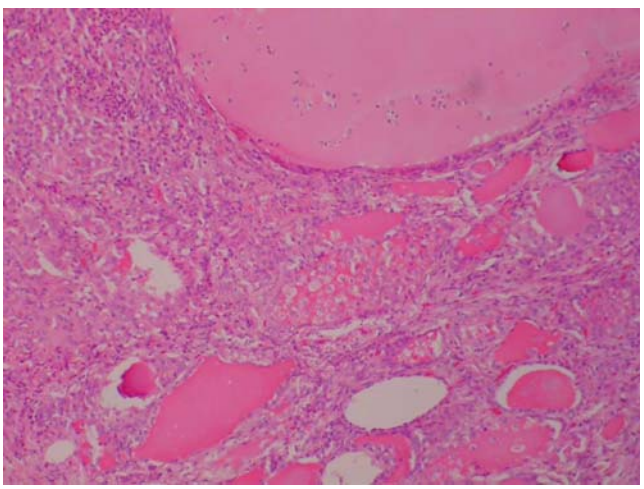

Fig. 1 Thyroid biopsy shows colloid-filled follicles, foreign body giant cells with engulfing colloid, inflammatory cells including lymphocytes, plasma cells, and micro-abscess with neutrophils. Areas of fibrosis in patches are associated with the inflammatory response. These findings are characteristics of GT

In another way, granuloma formation occurs as a result of a Th1-type immune response and characterized by infiltrate of activated macrophages and $CD4^+$ T lymphocytes. Interferon-γ, TNF-α, interleukin (IL)-12, and IL-18 play an important role in this granulomatous reactions. Based on these physiological aspects, the anti-TNF-α therapy may be indicated in patients with refractory sarcoidosis. Favorable response has been reported with infliximab [14]. In contrast, a worsening of sarcoidosis, even its induction, may be triggered with etanercept [1–5]. Other granulomatous reactions have been reported [6–13]. Differences in the mode of neutralizing TNF-α action between these TNF-α antagonist may be implicated in the genesis of granulomatous reaction. Infliximab is an anti-TNF-α monoclonal antibody and etanercept is a recombinant TNF receptor/IgG fusion protein. Infliximab binds both soluble and transmembrane TNF, whereas etanercept has a fourfold lower binding affinity for transmembrane TNF [15]. Infliximab bind TNF in a fast and irreversible fashion in vitro. In contrast, etanercept has both high on-binding and high off-binding kinetics, shedding about 50% of soluble TNF and 90% of transmembrane TNF only 10 min after binding [15]. Infliximab, after binding to membrane-anchored TNF on monocytes or lymphocytes, activate complement and cause antibody-dependent cellular cytotoxicity via their Fc tail [15].

There are similarities between other previous cases and the present one with granulomatous diseases associated with etanercept treatment. In this report, a GT was developed. Clinical features of GT are well-known and include thyroid pain with symptoms of hyperthyroidism, suppressed levels of TSH, low thyroid uptake of radioactive iodine, and elevated erythrocyte sedimentation rate. Diagnosis is based on clinical and laboratory data. Tissue diagnosis is rarely needed. Other granulomatous diseases are rarely necessary to exclude based mainly on combined clinical–pathological criteria, i.e., sarcoidal or tuberculous thyroiditis.

In summary, we report a case with RA who developed GT during etanercept therapy. Probably, this is the first case report of this association.

Disclosures None.

References

1. Gonzalez-Lopez MA, Blanco R, Gonzalez-Vela MC et al (2006) Development of sarcoidosis during etanercept therapy. Arthritis Rheum 55:817–820
2. Verschueren K, Van Essche E, Patrick V et al (2007) Development of sarcoidosis in etanercept treated rheumatoid arthritis patients. Clin Rheumatol 6:1969–1971
3. Ishiguro T, Takayanagi N, Kurashima K et al (2008) Development of sarcoidosis during etanercept therapy. Intern Med 47:1021–1025
4. Farah RE, Shay MD (2007) Pulmonary sarcoidosis associated with etanercept therapy. Pharmacotherapy 27:1446–1448
5. Toussirot E, Pertuiset E, Kantelip B et al (2008) Sarcoidosis occurring during anti-TNF-alpha treatment for inflammatory rheumatic diseases: report of two cases. Clin Exp Rheumatol 26:471–475
6. Kudrin A, Chilvars ER, Ginawi A et al (2007) Sarcoid-like granulomatous disease following etanercept treatment for rheumatoid arthritis. J Rheumatol 34:648–649
7. Vavricka SR, Wettstein T, Speich R et al (2003) Pulmonary granulomas after tumor necrosis factor α antagonist therapy. Thorax 58:278–279
8. Phillips K, Weinblatt M (2005) Granulomatous lung disease occurring during etanercept treatment. Arthritis Rheum 53:618–620
9. Oh J, Arkfeld DG, Horwitz DA (2005) Development of Crohn's disease in a patient taking etanercept. J Rheumatol 32:752–753
10. Hashkes PJ, Shajrawi I (2003) Sarcoid-related uveitis occurring during etanercept therapy. Clin Exp Rheum 21:645–646
11. Farah M, Al Rashidi A, Owen DA et al (2008) Granulomatous hepatitis associated with etanercept therapy. J Rheumatol 35:349–351
12. Hu S, Cohen D, Murphy G et al (2008) Interstitial granulomatous dermatitis in a patient with rheumatoid arthritis on etanercept. Cutis 81:336–338
13. Deng A, Harvey V, Sina B et al (2006) Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. Arch Dermatol 142:198–202
14. Doty JD, Mazur JE, Judson MA (2005) Treatment of sarcoidosis with infliximab. Chest 127:1064–1071
15. Scallon B, Cai A, Solowski N et al (2002) Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 301:418–426