

# Wegener's Granulomatosis with a Possible Thyroidal Involvement

Hakan Ozdogu, MD; Can Boga, MD; Filiz Bolat, MD; and Melek Eda Ertorer, MD  
Adana, Turkey

Wegener's granulomatosis (WG) is an autoimmune disorder characterized by the involvement of many organ systems. In patients with refractory disease, the efficacy of cyclophosphamide, corticosteroids and infliximab has been reported recently. Even in cases with serological response, disease progression has still been observed. Herein, we report a case of WG, most likely accompanied with subacute granulomatous thyroiditis while the patient was on cyclophosphamide, corticosteroid and infliximab therapy. As far as we know, this is the first time that such a copresentation has been observed, suggesting that mechanisms other than T-cell-mediated cytotoxicity may be important in the pathogenesis of granulomatous thyroiditis.

**Key words:** infliximab ■ subacute thyroiditis ■ Wegener's granulomatosis

## INTRODUCTION

Wegener's granulomatosis (WG) is a disease that usually cannot be cured by high-dose immunosuppressive therapy.<sup>1</sup> The effectivity of combination therapy with cyclophosphamide, corticosteroids and infliximab (a blocker of tumor necrosis factor- $\alpha$ ) in patients with relapsed and refractory WG leading to clinical and serological improvement has been confirmed by several reports before.<sup>1-3</sup>

Subacute granulomatous thyroiditis is an uncommon and self-limited cause of thyrotoxicosis, presenting with neck pain and tenderness at the thyroidal region. Viral infections or postviral inflammatory processes are claimed to play a role in its pathogenesis.<sup>4</sup> Until now, there has been no case reported to have subacute granulomatous thyroiditis associated with WG.

Herein, we present a case of refractory WG in a patient who developed a granulomatous thyroiditis while using the above mentioned combination therapy.

## CASE

A 54-year-old man with pulmonary renal syndrome was diagnosed with WG in our center in April 2003. A biopsy specimen from his sinus was reported as granulomatous with accompanying vasculitis (Figure 1). Although he received plasma exchange (a total of 11 procedures), cyclophosphamide pulse therapy (Endoxan®, Baxter Oncology GmbH, Halle, Germany, 1 g/m<sup>2</sup> for four months) and corticosteroids (Prednol®, methyl prednisolone, Mustafa Nevzat Ilac AS, Istanbul, Turkey) 2 mg/kg per day for a month with subsequent tapering of the dose, his renal functions deteriorated and a hemodialysis program was begun. Laboratory findings of WG, including antineutrophil cytoplasmic antibodies (ANCA, subtype PR3) and organ-specific disease, persisted in his blood samples. After four infusions of cyclophosphamide, remission was finally achieved.<sup>5</sup> An improvement in sinus symptoms was documented clinically, and a regression of pulmonary nodules was observed with high-resolution computed tomography. Microscopic hematuria with dysmorphic red blood cells disappeared, and his serum creatinine

© 2006. From the Division of Hematology (Ozdogu, Boga), Department of Pathology (Bolat), and Division of Endocrinology and Metabolism (Ertorer), Baskent University School of Medicine, Adana Medical Center, Adana, Turkey. Send correspondence and reprint requests for *J Natl Med Assoc*. 2006;98:956-958 to: Dr. Can Boga, Baskent University School of Medicine, Adana Medical Center, Division of Hematology, Dadaloglu Mahallesi Sokak. 39, No. 6 Yuregir 01250, Adana, Turkey; phone: +903223272727-2164; fax: +903223271274; e-mail: drcanboga@hotmail.com

levels decreased from 6.0 mg/dl to 2.1 mg/dl. Five months after the first admission, while he was receiving cyclophosphamide pulse therapy, and tapering the corticosteroid dose from 40 mg to 5 mg per day renal function again began to fall, creatinine levels rose from 2.1 mg/dl to 7.5 mg/dl within a month. Nephritic urinary sediment and new pulmonary infiltrates were observed. Standard therapy with cyclophosphamide (2 mg/kg p.o. per day) and corticosteroid therapy (methyl prednisolone 2 mg/kg) was reinitiated. The institution of standard therapy did not improve the disease activity over the following two months. The addition of intravenous immunoglobulin therapy (500 mg/kg for once) failed to induce remission. Eight months after the first admission, infliximab therapy (Remicade; Essex Pharma, Munich, Germany) at a dose of 5 mg/kg was added to standard therapy. Although there was evidence of regression of the pulmonary nodules, infliximab was withdrawn after the first infusion, due to a pseudomonal infection of the nasopharynx. He was treated with a 20-day course of meropenem (6 g per day) and amikacin (1 g per day). The cure of infection was confirmed with negative cultures.

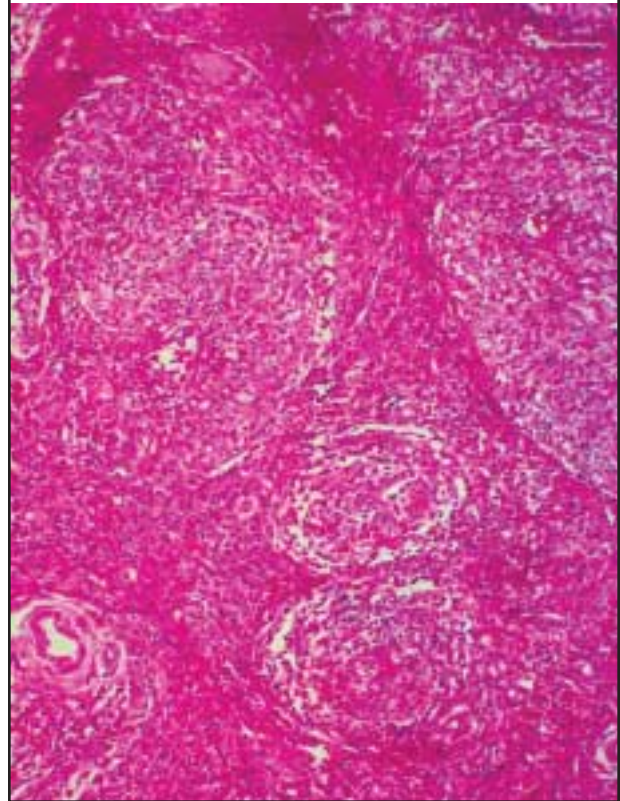
One month following infliximab therapy, while serum ANCA (subtype PR3) were negative and WG was in a stable condition, the patient began to suffer from neck pain. He had difficulties swallowing and tenderness in the thyroidal region on palpation. Bed-side thyroidal ultrasonography and fine-needle aspiration biopsy (FNAB) was performed. The patient objected to have a scintigraphic imaging due an emotional imbalance. Serologic markers of inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found to be elevated. Thyroid nodules were detected by ultrasonography. Serum thyroid-stimulating hormone levels were:

- TSH: 0.13 uIU/ml (0.30–4.94 uIU/ml),
- free triiodothyronine (fT<sub>3</sub>): 2.91 pmol/L (2.22–5.34 pmol/L) and
- free thyroxine (fT<sub>4</sub>): 19.06 pmol/L (9.00–25.00 pmol/L).

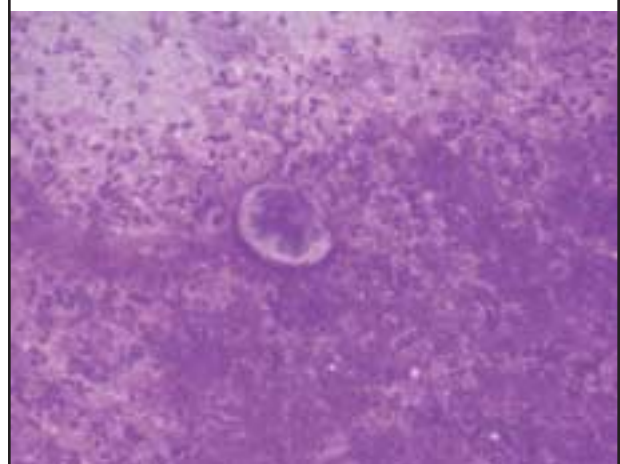
Thyroidal autoimmune antibodies were within normal limits: antithyroglobulin (ATA) 65.73 IU/ml (1.40–78.00 IU/ml) and antithyropoxidase (anti-TPO) 2.2 IU/ml (0.00–12.00 IU/ml). No bacterial colonization was observed in the cultures of specimen taken by FNAB, which ruled out the bacteria as the causative agent. The cultures were kept long enough to adequately check for mycobacterium tuberculosis. An acid-fast stain for mycobacterium tuberculosis gave negative results. Serological tests for viral etiologies, including hepatitis-B and hepatitis-C virus, parvovirus B19, cytomegalovirus, Epstein-Barr virus,

human immunodeficiency viruses 1 and 2, and herpes virus types 1 and 2, were also negative. FNAB of the thyroid revealed granulomas that were typical for WG (Figure 2). Corticosteroid dose was maintained at 40 mg per day. The neck pain relieved, he maintained an euthyroid state, and WG was stable during the following three months.

**Figure 1. Wegener's granulomatosis, ill-defined granulomas containing inflammatory cells (H.E. x100)**



**Figure 2. Granulomatous inflammation, mixed inflammatory cell types and multinucleated giant cells (fine-needle aspiration biopsy x200)**



## DISCUSSION

Combination therapy with cyclophosphamide, corticosteroids and infliximab has renewed the therapeutic options in relapsing and refractory WG with a reduction of serum CRP, antineutrophil cytoplasmic antibodies.<sup>1-3</sup> However, it has been reported that WG may be less responsive, and extensive organ involvement despite serological response can be observed during this treatment.<sup>6,7</sup>

Subacute granulomatous thyroiditis is presumed to be caused by a viral infection or a postviral inflammatory process. The hallmarks of subacute granulomatous thyroiditis are thyrotoxicosis and tenderness at the neck, accompanied with elevated ESR, CRP and a low 24-hour <sup>131</sup>I uptake (<5%) at the thyroidal region.<sup>5</sup> Although low levels of thyroidal autoantibodies may appear during the course of disease, they never reach levels seen in autoimmune thyroiditis. Therefore, it is not considered to be an autoimmune disease.<sup>8</sup> Most of the patients with subacute granulomatous thyroiditis report an upper respiratory tract infection shortly preceding the onset of thyroiditis. Coxsackievirus, mumps, measles and adenovirus are claimed to play a role in the pathogenesis.<sup>9</sup> The disorder is claimed to result from a subclinical viral infection that provides an antigen, either of viral origin or virus-induced host tissue damage. This antigen binds to HLAB35 molecules on macrophages and antigen-HLAB35 complex activates cytotoxic T lymphocytes. As thyroid follicular cells have some structural similarities with infection-related antigen, damage begins on these cells.<sup>10</sup> FNABs reveal neutrophils, histiocytes, lymphocytes, formation of granulomas composed of giant cells, disruption and the collapse of thyroid follicles and necrosis of follicular cells.<sup>9</sup>

We believe that the typical clinical and laboratory findings and the dramatic response to corticosteroids all favored the diagnosis of subacute granulomatous thyroiditis in this subject. However, our inability to perform scintigraphical imaging was a limitation in obtaining a definitive diagnosis. The unexpected presentation of a painful thyroiditis, clinically resembling subacute granulomatous thyroiditis, made us wonder whether this might be another specific involvement of WG or not. Although the literature on subacute thyroiditis does not always confirm the presence viral titres, the negative results of both viral and bacterial cultures, performed on serum as well as the tissue specimen, supported our hypothesis. Considering the important role of T lymphocytes in the pathogenesis of subacute granulomatous thyroiditis, the administration of a combination of immunosuppressive therapy, dominantly suppressing T-cell-mediated immunity, would possibly not result in the progression of this type of thyroiditis. However, FNAB of the thyroid was in

favor of subacute granulomatous thyroiditis as well as WG. We therefore propose that this may be the thyroidal involvement of a refractory WG.

As far as we know, this is the first case report proposing a possible association between WG and subacute granulomatous thyroiditis. It may give new insights to the pathogenesis of subacute granulomatous thyroiditis, and opens the possibility that mechanisms other than T-cell-mediated immunity may play a role.

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