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A case of Graves' disease developing with exacerbation of sarcoidosis

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Abstract. A 53-year old female was referred to our hospital with bilateral abnormal shadow in the chest X-ray. Computed tomography revealed multifocal ill-defined densities and thickening of bronchial wall and pulmonary vessels by fine nodules combined with massive enlargement of bilateral mediastinal and hilar lymph nodes. Analyses of bronchoalveolar lavage fluid and transbronchial lung biopsy specimen showed the increase in CD4/CD8 ratio and the presence of non-caseating granulomas, respectively. In addition, serum angiotensin-converting enzyme was extremely high, leading to the diagnosis of sarcoidosis. Simultaneously, she complained of palpitation and sweating. Endocrinological examination showed comorbid hyperthyroidism without anti-TSH receptor antibody (TRAb). In the first 2-3 months, pulmonary shadow gradually disappeared without steroid administration. In parallel, serum thyroid hormone levels were gradually normalized in the beginning, but increased after 3 months with an appearance of TRAb. After initiation of treatment with antithyroid agent, hyperthyroidism was improved within 9 months, and changed into hypothyroidism thereafter. The clinical course of this rare case suggest that immunological storm by exacerbation of sarcoidosis may trigger the onset of autoimmune thyroid disease, in which hyperthyroidism with stimulating type of TRAb subsequently changed into hypothyroidism with blocking-type TRAb. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (4): 318-324)*

Key words: sarcoidosis, Graves' disease, eosinophil

Introduction

Although the etiology of sarcoidosis is unknown, Th1-mediated inflammatory process appears to be essential for the granuloma formation in sarcoidosis (1-3). In addition, sarcoidosis is often associated with increased humoral response and hyperglobulinemia (4), resulting in increased autoimmune comorbidities (5, 6). In this respect, there are a number of reports showing the close association between autoimmune thyroid disease (AITD) and sarcoidosis (6-14). A remarkably high incidence of thyroid autoantibodies against thyroid peroxidase (TPO-Ab), purified thyroglobulin (Tg-Ab) and TSH receptor (TRAb) was found in patients with sarcoidosis (8, 10, 14). A significantly higher prevalence of Hashimoto's thyroiditis with clinical hypothyroidism and Graves' disease has also been reported in sarcoidosis (10, 14). Isern et al. (11) described that AITD usually does not develop during the period of active sarcoidosis, but, in most of cases, sarcoidosis preceded between 4 months to 17 years the development of AITD. A nationwide case-control study in Taiwan

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also revealed that the diagnosis of sarcoidosis usually preceded that of autoimmune comorbidities including AITD (6). Here, we present the rare case of Graves' disease which was diagnosed simultaneously with exacerbation of sarcoidosis. Hyperthyroidism gradually ameliorated in the beginning in parallel with radiographic improvement of pulmonary sarcoidosis, but deteriorated after 3 months with an appearance of stimulating type of anti-TSH receptor antibody (TSAb). Furthermore, hyperthyroidism subsequently changed into hypothyroidism with blocking-type TRAb (TSBAb). We discuss whether immunological similarity between sarcoidosis and AITD may cause such comorbidity.

Case Report

A 53-year-old female was referred to our hospital with bilateral abnormal shadow in the chest X-ray on August 23 in 2015 (Figure 1A). Her medical history revealed that she had been complaining of palpitation and sweating one month before her first visit. In addition, aggregated miliary papules appeared on both knees just around the first visit. She did not have fever, cough, sputum and shortness of the breath. Her past history showed no abnormality in the chest X-ray one year before the first visit, and no allergic disease such as rhinitis, urticaria or asthma.

Physical examination on admission showed that she had a diffuse soft goiter and hand tremor, but no exophthalmos was observed. Miliary papules were aggregated on both knees (Figure 2D). Her height was 161 cm and weight was 54.0 kg. Blood pressure was 136/70 mmHg and heart rate was 120/min. Laboratory findings revealed a red blood cell count of 494 x 10^4/mm^3, hemoglobin at 12.8 g/dl, and hematocrit at 37.8%. The white blood cell count was 5400 /mm^3 with 8% eosinophils, and her platelet count was 28.4 x 10^4/mm^3. Serum electrolytes were the following: Na 141 mEq/l; K 4.1 mEq/l; Cl 104mEq/l and Ca 9.5 mg/dl. Serum BUN was 12.3 mg/dl; creatinine, 0.57 mg/dl; and uric acid, 6.0 mg/dl. Total serum protein was 8.2 g/dl with 55.1% albumin; AST, 22 IU/l; ALT, 14 IU/l; LDH, 175 IU/l; γ-GTP, 42 IU/l; and total cholesterol, 206 mg/dl.

Computed tomography (CT) revealed multifocal ill-defined densities and thickening of bronchial wall and pulmonary vessels by fine nodules combined with massive enlargement of bilateral mediastinal and hilar lymph nodes (Figure 1B-E). Analysis of bronchoalveolar lavage fluid (BALF) revealed elevated lymphocyte (70.5%) and eosinophil (6.5%) counts and a high CD4/8 ratio (6.74), compared to the Japanese control values (15, 16). Furthermore, trans-

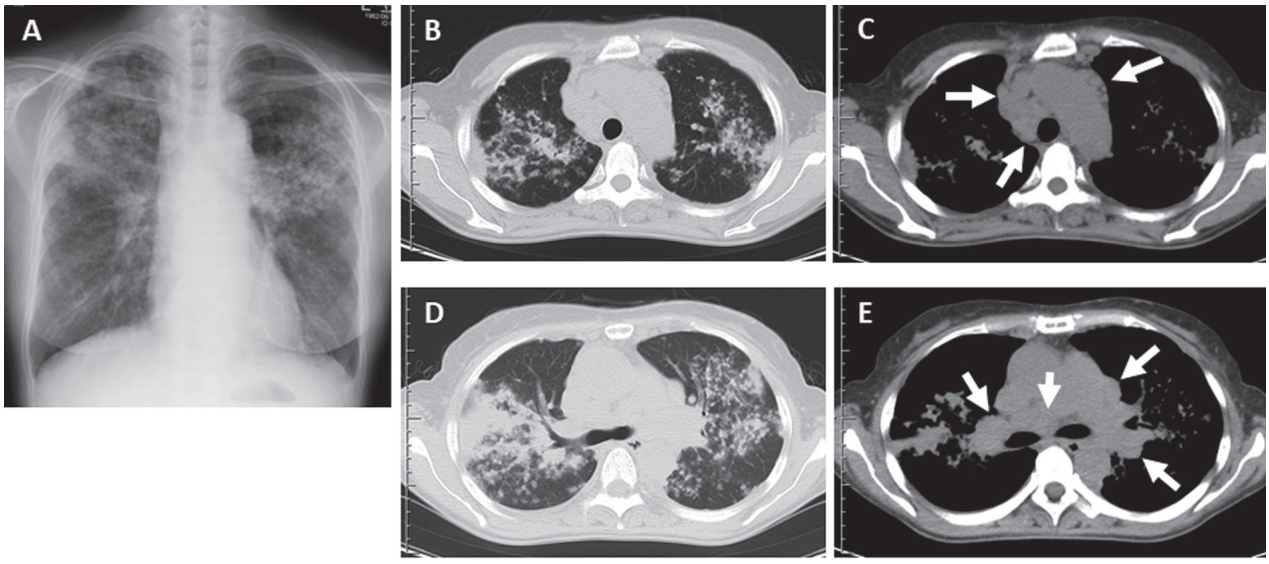

Fig. 1. Chest X-ray (A) and computed tomography (CT) imaging (B-E) at first visit. CT scan revealed multifocal ill-defined densities and thickening of bronchial wall and pulmonary vessels by fine nodules (B, D). Arrows indicate massive enlargement of bilateral mediastinal and hilar lymph nodes (C, E)

bronchial lung biopsy specimen showed the presence of non-caseating granulomas with mild eosinophil infiltration around the granuloma (5-10/1HPF) (Figure 2A-C). Skin biopsy from miliary papules on the left knee also revealed the accumulation of non-caseating granulomas in the dermis (Figure 2E, F). In addition, serum angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL2R) was extremely high (ACE; 70.0 IU/L [normal: 7.7-29.4], sIL2R; 5360 U/mL [normal: 124-566]), leading to the diagnosis of sarcoidosis (Figure 3).

On the other hand, as shown in Figure 3, serum free T3 and free T4 was high, whereas serum TSH was suppressed. Although TRAb was negative, high ^{123}I uptake (76.3% in 24h) led us to diagnose comorbid Graves' disease without TRAb (Figure 4A). The ultrasonography revealed the enlargement of thyroid gland with heterogeneous echotexture and hypervascular pattern in the color Doppler imaging, which is consistent with Graves' disease (Figure 4B-D).

The clinical course was shown in Figure 3. Beta-blocker was initiated, while, in the first 2-3 months, pulmonary shadow and aggregated miliary papules on both knees were gradually disappeared without steroid treatment. In parallel, serum thyroid hormone levels were gradually decreased in the beginning, but increased after 3 months with an appearance of TSAb. After initiation of treatment with antithyroid agent, hyperthyroidism was improved within 9 months, and changed into hypothyroidism with TSBAb thereafter. Therefore, antithyroid agent was discontinued and, instead, levothyroxine was initiated.

Discussion

Among thyroid autoimmunity, Hashimoto's thyroiditis is Th1 predominant, while Graves' disease is a Th2-predominant disease (17). In this context, it is of interest that Hashimoto's thyroiditis is frequently aggravated from 1 to 4 months postpartum, a period corresponding to the rebound of cellular immunity (Th1), and Graves' disease frequently develops or relapses from 4 to 12 months postpartum through the rebound of humoral immunity (Th2) (18). Similarly,

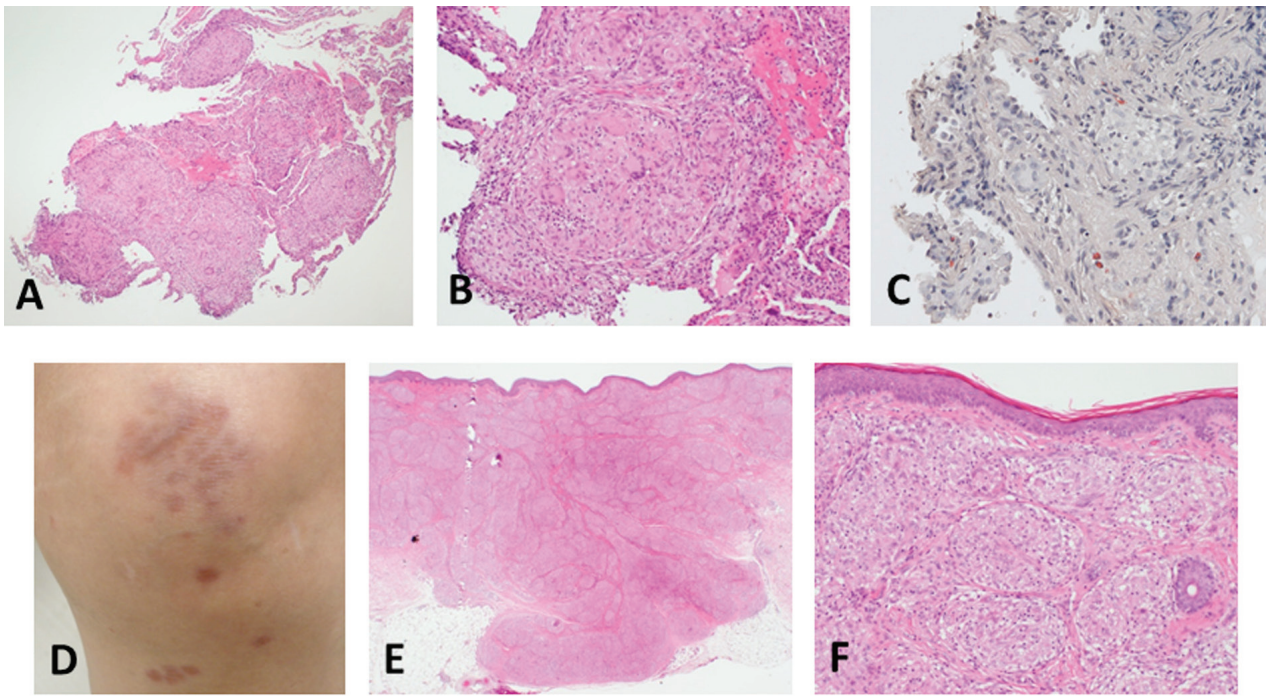

Fig. 2. Histopathological findings of transbronchial lung biopsy specimen (A, B) revealed the presence of non-caseating granulomas. Direct fast scarlet staining (C; x200) showed mild eosinophil infiltration around the granuloma as indicated by red cytoplasm (5-10/1HPF). Skin biopsy from miliary papules on the left knee (D) also revealed the accumulation of non-caseating granulomas in the dermis (E, F). Hematoxylin and eosin staining (A, E; x20, B, F: x100)

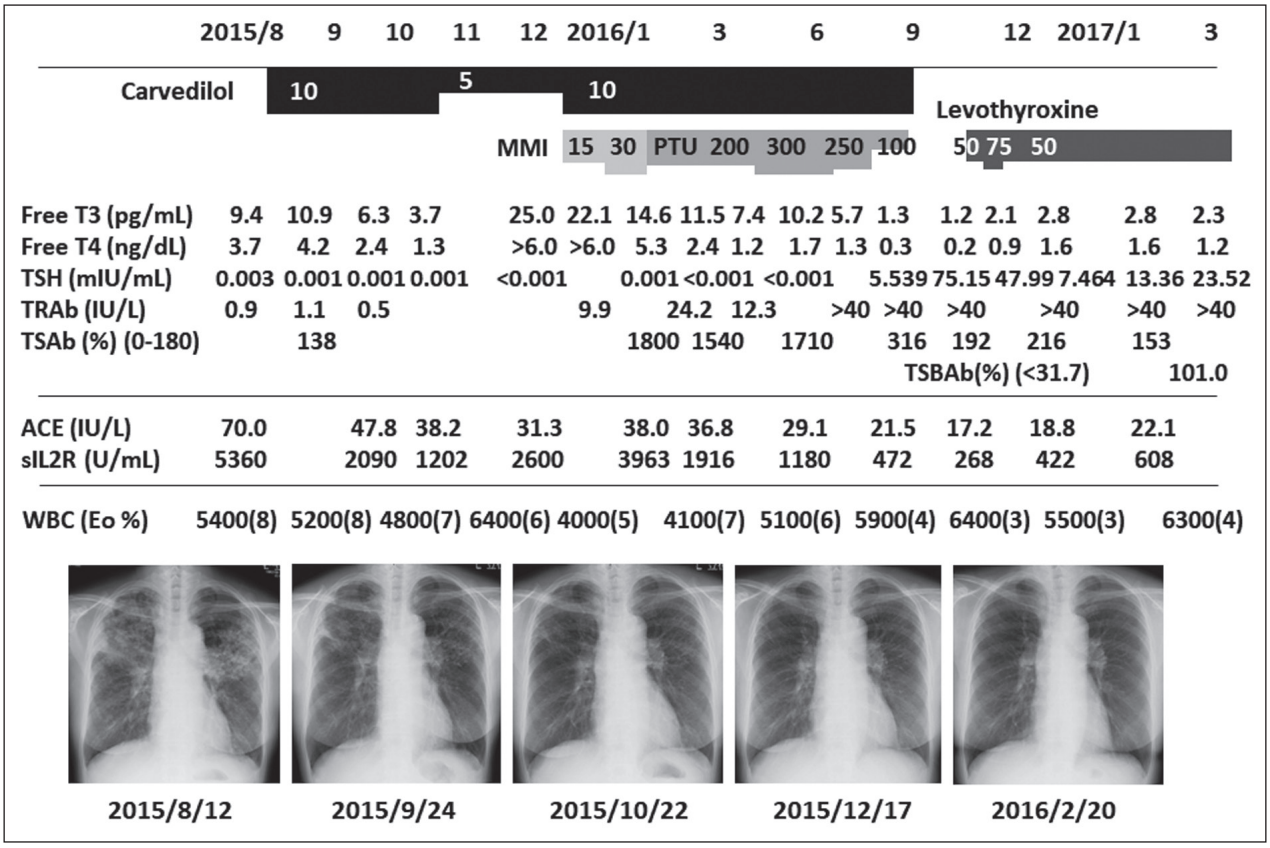

Fig. 3. Clinical course. Sarcoidosis was spontaneously remitted within 3-4 months. In parallel, serum thyroid hormone levels were gradually normalized in the beginning, but increased after 3 months with an appearance of TSAb. After initiation of treatment with antithyroid agent, hyperthyroidism was improved within 9 months, and changed into hypothyroidism with TSBAb thereafter

Takeoka et al. (19) demonstrated that seasonal allergic rhinitis induced an increase in TRAb and aggravated the clinical course of Graves' disease. They proposed that allergic rhinitis is a typical Th2-associated disease and thereby evokes Th2-dependent autoantibody production in the thyroid gland, namely TRAb. Since sarcoidosis is thought to be a Th1-predominant disease (1, 2, 3), a significantly higher prevalence of Hashimoto's thyroiditis in patients with sarcoidosis is convincing (10, 14). In contrast, difference in Th1/Th2 state between sarcoidosis and Graves' disease may not solely explain their comorbidity. However, there is one study examining the Th1/Th2 balance and its relation to disease development in pulmonary sarcoidosis. HLA-DRB1*0301 positive Scandinavian patients exhibited a reduced expression of proinflammatory Th1 cytokines and a relative shift towards anti-inflammatory Th2 cytokines may relate to the spontaneous disease resolution in pulmonary sarcoidosis (20). Since the spontaneous disappearance of the pulmonary shadow was observed in the present case, a relative shift towards Th2-associated immunity may occur at some point to cause the development of Graves' disease in this patient. Alternatively, Idali et al. found that a reduced expression of regulatory T cell associated genes in BALF CD4+ T cells of sarcoidosis patients (21). The diminished regulatory T cell suppressor function may allow the development of autoimmune comorbidities including Graves' disease (3). On the other hand, HLA-B8 is reportedly associated with spontaneous resolution (22) or shorter duration of disease (23) in sarcoidosis. Since HLA-B8 is known to be one of the genes susceptible to Graves` disease (24), genetic background such as HLA-B8 may be attributable to the spontaneous resolution in sarcoidosis and the development of Graves' disease.

We found mild eosinophilia (8%) in plasma and elevated eosinophil count (6.5%) in BALF at the exacerbation of sarcoidosis in our patient. Peripheral

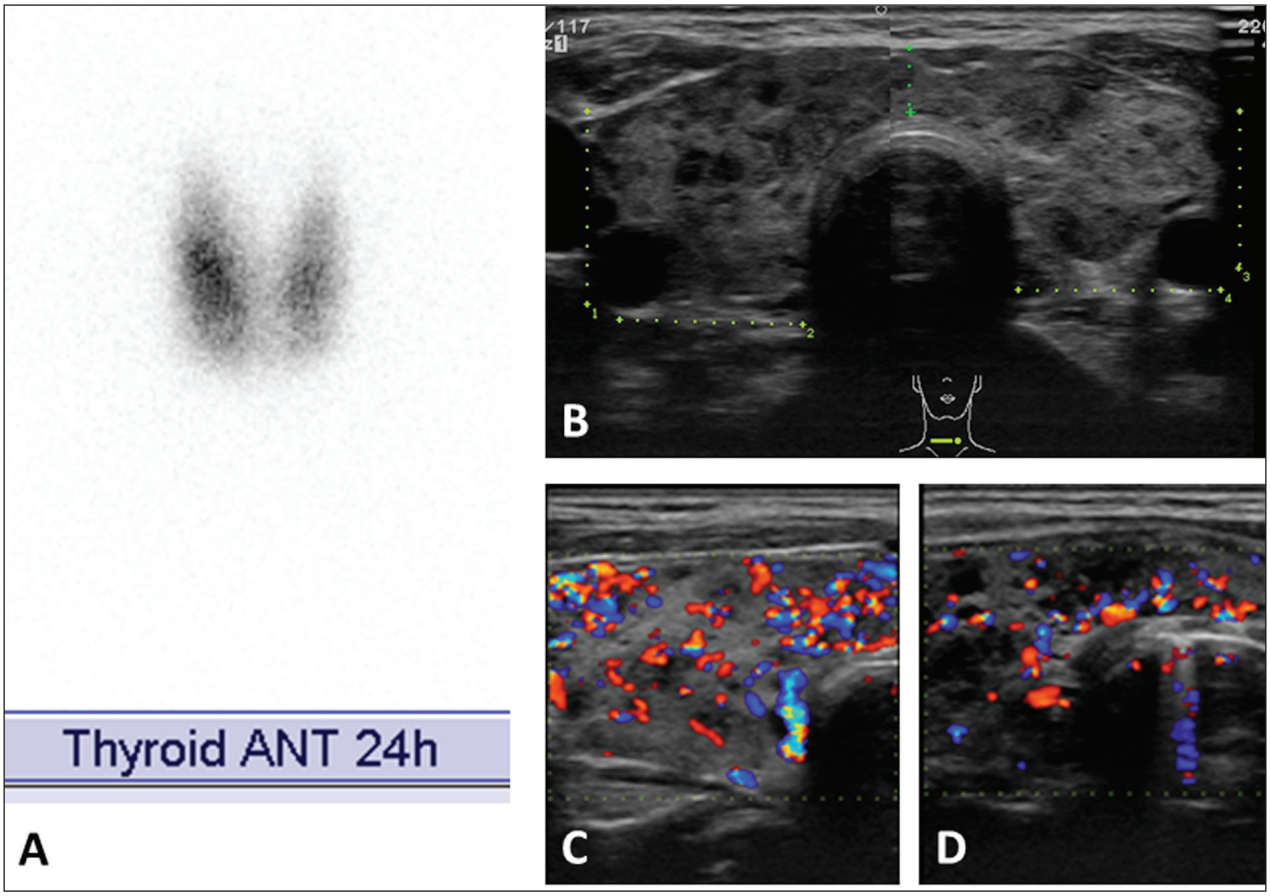

Fig. 4. High ^{123}I uptake (76.3% in 24h) led us to diagnose comorbid Graves' disease (A). The ultrasonography revealed the enlargement of thyroid gland with heterogeneous echotexture (B) and hypervascular pattern in the color Doppler imaging (C, D)

blood eosinophilia (>4%) occurs 41% of 95 patients (25) or 35.4% of 178 patients with sarcoidosis (26). Thus, peripheral blood eosinophilia is common in sarcoidosis. In contrast, several studies showed that most of patients with sarcoidosis showed 1% or less eosinophils in BALF (27-29). Takahashi et al. (26) also reported that, among 178 patients with sarcoidosis examined retrospectively in their clinic-based study, the highest eosinophil percentage in BALF was 2.6%. Ziegenhagen et al. (28) demonstrated that an increased percentage of BALF neutrophils (>3%) and eosinophils (>1%) could reflect an ongoing inflammatory process in pulmonary sarcoidosis with progressive potential. On the other hand, 4 exceptional cases of pulmonary sarcoidosis with remarkably elevated eosinophils in BALF (15.2-94.2%) showed ground-glass opacities in chest CT scan and were considered to be associated with eosinophilic pneumonia (26, 30-32). Among these cases, Tani et al. (32) reported increased both Th1 (IFN-γ) and Th2 (IL-4 and IL-5) cytokines in BALF. They found that corticosteroid therapy reduced eosinophils and Th2 cytokines in BALF along with pulmonary infiltration, while BALF Th1 cytokine and pulmonary nodular shadow with hilar/mediastinal lymphadenopathy did not show significant changes, suggesting a close association between BALF Th2 cytokines and eosinophilic pneumonia, but not pulmonary sarcoidosis. Our patient showed no ground-glass opacities on the chest CT scan and no sign of eosinophilic pneumonia in the histopathology. It should be clarified whether an elevation of BALF eosinophil in our patient is associated with activation of Th2 cytokines.

In the first 2-3 months, TRAb was negative and serum thyroid hormone levels gradually normalized without antithyroid drug treatment in parallel with

radiographic improvement of pulmonary sarcoidosis. This raises the possibility that thyroid involvement of sarcoidosis may cause hyperthyroidism in the beginning. Thyroid involvement is rare and up to 4.5% in post-mortem studies of patients with systemic sarcoidosis (33). Thyroid sarcoidosis usually presents as a progressive painless thyroid enlargement with unaffected hormonal status, but could exhibit hyperthyroidism or sometimes coexists with Graves' disease (33). Concomitant thyroid sarcoidosis in Graves' disease may contribute to the resistance to antithyroid drugs and radioiodine therapy (34-37, 38). Since antithyroid drug appeared to be effective after deterioration of hyperthyroidism with appearance of TRAb, it is likely that thyroid sarcoidosis, if so, was mostly remitted before deterioration of hyperthyroidism. Although the patient rejected thyroid aspiration biopsy, the histopathological examination should have been done to clarify the thyroid involvement of sarcoidosis especially in the first 2-3 months, which is a limitation of this study.

About one-third of patients with Graves' disease have TSBAb (39). Although TSAb and TSBAb are often both present in patients with Graves' disease, coexisting TSBAb does not usually affect TSAb-induced hyperthyroidism (39). However, a drastic change in the nature of TRAb sometimes influences the clinical course of Graves' disease, although the reason for such change is uncertain. Tamai et al. (40) have shown that hypothyroidism occurs in 5-20% of Graves' disease patients previously treated with antithyroid drugs and that TSBAb may account for such hypothyroidism in approximately one-third of patients. Miyauchi et al. (41) reported a typical case showing that hyperthyroidism switched into the hypothyroidism due to the changes in the predominance of the nature of TRAb, i.e. from TSAb to TSBAb, consistent with the present case. To the best of our knowledge, this is the first report of Graves' disease comorbid with sarcoidosis, in which hyperthyroidism with TSAb switched into hypothyroidism with TSBAb.

Our patient showed a cutaneous manifestation in the beginning. Consistent with the present case, Anolik et al. (42) suggest a high rate of thyroid dysfunction in patients with cutaneous sarcoidosis. Although cutaneous lesions were spontaneously remitted in parallel with disappearance of pulmonary shadow, it should be carefully monitored for recurrence of cutaneous and pulmonary lesions and for their association with changes in thyroid dysfunction.

In conclusion, we report the rare case of Graves' disease developing concomitantly with exacerbation of sarcoidosis. The immunological storm of sarcoidosis could induce the production of thyroid autoantibody, which subsequently changed from TSAb to TSBAb. This case highlights the need for a careful assessment of thyroid function and thyroid autoantibodies in patients with sarcoidosis.

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