Abstract. We report the case of a 64-year-old woman with rheumatoid arthritis (RA) associated with high grade fever, malaise, and painless swelling of thyroid gland. Laboratory findings showed severe systemic inflammatory reactions, including increases in various cytokines such as IL-6. Gallium-67 citrate imaging revealed intense uptake in the painlessly enlarged thyroid gland. Histologically, biopsied specimens of thyroid showed diffuse amyloid infiltrations, which included amyloid A (AA) protein. Biopsies of rectum and stomach revealed similar amyloid depositions, indicating that the amyloid had a secondary origin, potentially due to RA. All clinical symptoms were relieved by intravenous pulsatile administration of methylprednisolone followed by oral prednisone, resulting in prolonged hypothyroid status. To our knowledge, this is the first case report in Japan describing painless thyroiditis with severe inflammatory reactions in amyloid goiter.

Key words: Painless thyroiditis, Amyloid goiter, Subacute thyroiditis-like syndrome, Interleukin-6 (IL-6), Rheumatoid arthritis

AMYLOID deposition in the thyroid is found in about 30-80% of patients with primary or secondary amyloidosis [1]. In a few patients with amyloidosis, the thyroid is enlarged and so-called amyloid goiter occurs. In most cases, thyroid function is normal [2, 3], but both hypo- and hyperthyroidism have been observed in patients with amyloid goiter [2, 4, 5]. To date, six cases of amyloidosis have been reported with symptoms resembling subacute thyroiditis [6-10] in Japan. In 1988, Ikenoue et al. [9] first used the term subacute thyroiditis-like syndrome (STLS) to describe a clinical state resembling subacute thyroiditis. All the reported patients developed severe thyroidal pain localized in the same site, with histological evidence of diffuse amyloid deposition. However, because of the limited number of cases, the definite clinical entity and pathogenesis of STLS remained unclear. Here, we report a patient with secondary amyloidosis due to rheumatoid arthritis (RA) with amyloid goiter accompanied by transient thyrotoxicosis followed by prolonged hypothyroid status resembling STLS. In particular, the patient had a nontender thyroid despite severe inflammatory reactions. To our knowledge, is the first such case report in Japan.

Material and Methods

Serum concentrations of TSH, free T4 (FT4), and free T3 (FT3) levels were measured by enhanced luminescent assay using commercially available kits. Anti-thyroid peroxidase (TPO) and anti-thyroglobulin antibodies were determined by RIA. TSH-binding inhibitory immunoglobulin (TBII) was measured with a radioreceptor assay. Thyroid-stimulating antibodies (TSAb) and thyroid stimulation blocking antibodies (TSBAb) were detected by RIA.
Serum levels of various cytokines such as Interleukin-6 (IL-6) [11], IL-1β, IL-2 tumor necrosis factor (TNF) and Interferon-γ were measured using an EIA method.

Case Report

A 64-year-old female was first diagnosed with RA at another clinic based on arthralgia in the bilateral joints of her hands and positive RA titers in April, 1992. On February 25, 1998, six years after diagnosis, she was first admitted to our hospital for exacerbation of RA. After admission, she received peroral prednisone (20 mg/day), which relieved her arthralgia and decreased RA activity, resulting in normalization of C-reactive protein levels. She was released on March 20 after 24 days. However, prednisone was stopped in September, 1999, due to development of vertebral compression fracture, which was considered to be an adverse effect of steroids. On October, 1999, the patient suddenly developed constant fever (ranging between 37 and 40°C) and progressive malaise. She was readmitted to our hospital on October 25, 1999, for idiopathic fever under tentative diagnosis of upper respiratory tract infection based on slight cough and sputum. At this time, the patient did not feel any arthralgia in her extremities, or pain or tenderness in her neck. She had not been taking excess iodine.

On physical examination at admission, her temperature was 39.2°C and pulse rate was 102 beats /min. Neither tonsils nor systemic lymph nodes showed swelling, and no definite cracks were heard on auscultation of her chest. Her abdomen was flat and soft with no mass or tenderness. Neither pain nor tenderness were noted in all joints of her extremities. Moderate diffuse goiter (estimated thyroid volume 58.2 cm³) with firm consistency and a nodular surface without tenderness or bruising was noted. She had no exophthalmos or pretibial edema.

Laboratory findings on admission revealed mild leukocytosis (9000/mm³; normal range 3100–8500 /mm³) and thrombocytosis (35.2 × 104/mm³; 12–35) in addition to moderate normocytic anemia (10.7 g /dl; 11.0–15.5 g/dl). Both CRP (24.4 mg/dl; 0.0–0.4 mg/dl) and erythrocyte sedimentation rate (ESR) (134 mm/h; 3–11 mm/h) were fairly high, accompanied by elevation of various cytokine levels such as IFN-γ (86 IU/ml; 10 >), TNF (140 pg/ml ; 6 >), IL-1β (58 pg/ml; 8 >), IL-2 (66 pg/ml; 50 >) and IL-6 (227 pg/ml; 25 >). These increased levels persisted after treatment with prednisolone on the 30th hospital day (74 IU/ml, 156 pg/ml, 50 pg/ml, 62 pg/ml and 218 pg/ml, respectively). Urinalysis revealed normal findings suggesting that urinary tract infection was unlikely.

Thyroid panel revealed elevated FT4 (3.10 ng/dl; 0.85–1.72 ng/dl) and FT3 (4.09 pg/ml; 2.31–4.07 pg/ml) levels associated with suppression in TSH levels (0.01 µU/ml; 0.32–4.57 µU/ml). Anti-thyroid peroxidase antibody (anti-TPOAb) and anti-thyroglobulin antibody (anti-TgAb) levels were both elevated (8.6 U/ml; normal <0.3 U/ml: 4.6 U/ml; <0.3 U/ml, respectively), while TBII (0.1%; normal <10), TSAb (80%; <180) and TSBAb (12%; <30%) were not detected.

Serum titers of antibodies to influenza, parainfluenza, mumps, measles, adenovirus, Epstein-Barr virus and coxsackie virus showed no change. She was positive for HLA A24, A31, B52, B54, DR4, DR15, DQ1 and DQ4. HLA typing did not reveal a BW 35 haplotype, a well-known marker of subacute granulomatous thyroiditis.

The clinical course after admission is shown in Fig. 1. Despite initiation of combined antibiotic therapy with piperacillin (4 g/day) and amikacin (200 mg/day), followed by meropenem trihydrate (1 g/day) and minocycline (200 mg/day), a fever of approximately 39°C still persisted. Chest X-ray and computed tomography (CT) of the chest, abdomen and pelvis did not reveal any fever-inducing foci such as pneumonia or abscess, but scintigraphy with gallium-67 (Ga-67) citrate revealed an intense focal uptake in an enlarged thyroid gland (Fig. 2), strongly implicating the thyroid as the focus. Neck CT revealed bilateral enlargement of the thyroid gland with scattered low density areas (Fig. 3) and the RAIU value examined on the 7th hospital day was low at 3.6% (24 h), consistent with destructive thyroiditis. Based on these laboratory data and imaging studies, a diagnosis of acute exacerbation of chronic autoimmune thyroiditis with nontender thyroid [12] was first suspected. Therefore, intravenous pulsatile administration of methylprednisolone (125 mg/day) for three days followed by peroral prescription of prednisone (60 mg/day) was initiated, resulting in marked reduction in her fever. Serum C-reactive protein
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levels concomitantly decreased to around 2 mg/dl after the 10th hospital day, and a mild relapse in inflammatory reaction occurred around the 55th hospital day.

After the 30th hospital day, her thyroxine level gradually decreased to below the normal range, together with a gradual rise in serum TSH level. Thus, levothyroxine sodium (T4; 50 μg/day) was prescribed for hormone replacement. Although transient normalization of T4 level occurred after initiation of T4 replacement, the level decreased again to overt hypothyroid status (0.49 ng/dl) after the 70th hospital day (Fig. 1). Throughout the observation period, the patient did not complain of pain or tenderness in her neck.

Needle biopsy specimens were obtained once from each quadrant of the thyroid for a total of four samples on the 25th hospital day. Hematoxylin-eosin staining of cell block material showed a predominance of amorphous eosinophilic material deposited in the stroma and in thickened blood vessel walls with few follicular cells (Fig. 4A). Congo red staining of the specimens was consistent with amyloid deposition, leading to the histological diagnosis of amyloid goiter (Fig. 4B). Calcitonin staining was negative and neoplastic cells were absent, which ruled out medullary carcinoma of the thyroid as a cause of the amyloid deposition. There was no evidence of subacute granulomatous thyroiditis such as the appearance of giant cells or of chronic lymphocytic thyroiditis such as the appearance of lymphocytic infiltrations. Histological examination with antihu-

Fig. 1. Clinical course and laboratory findings. Despite the initiation of combined antibiotic therapy, a fever of approximately 39°C persisted. Therefore, intravenous pulsatile administration of methylprednisolone (125 mg/day) over three days followed by a peroral prescription of prednisone (60 mg/day) was initiated, resulting in marked lowering of temperature. Serum C-reactive protein levels concomitantly decreased to around 2 mg/dl after the 10th hospital day, while a mild relapse in inflammatory reaction occurred around the 55th hospital day. After the 30th hospital day, her thyroxine level gradually decreased to below the normal range, together with a gradual rise in serum TSH level. Levothyroxine sodium (T4; 50 μg/day) was prescribed for hormone replacement. However, after the 70th hospital day, the thyroxine level again decreased to overt hypothyroid status (0.49 ng/dl), despite transient normalization after initiation of T4 replacement.
man amyloid A protein (AA) revealed diffuse deposition of AA protein in the thyroid gland. In addition, biopsies of rectum and stomach revealed similar amyloid deposition consisting of AA protein, indicating that the amyloid was of secondary origin [13], potentially from chronic inflammation due to RA.

Discussion

In a review of five patients with amyloid goiter exhibiting symptoms resembling subacute thyroiditis, Ikenoue et al. [9] first used the term STLS to describe this novel disease entity, and described several
characteristics of STLS in amyloid goiter: first, thyroid pain is not creeping; Second, in contrast to other thyroid disorders, STLS in amyloid goiter seems to occur more frequently in men than in women; third, the associated diseases varied, showing inflammatory bowel disease in two, tuberculosis in two, and RA in one. Recently, Nagai et al. [10] reported an additional case associated with hypersensitivity vasculitis, while our case was accompanied by RA. In our case, it was unlikely that reactivation of RA was due to withdrawal of steroids, thus inducing severe inflammatory reactions including elevated serum IL-6 levels, since the patient felt no joint pain or tenderness, nor was there no joint uptake in Ga-67 scintigraphy taken during the active inflammatory phase. To date, there have been no reports of STLS in amyloid goiter from countries other than Japan.

The pathogenesis of STLS in amyloid goiter has yet to be elucidated. Miaskiewics et al. [14] reported amiodarone-induced thyrotoxicosis with enlarged tender thyroid gland, which is clinically and histologically similar to STLS in amyloid goiter [15]. Amiodarone may induce destructive thyroiditis with an increase in serum IL-6 [16], which is well known to induce acute inflammatory reactions, including increased CRP and accelerated ESR [17]. Furthermore, serum IL-6 concentrations also increased in patients with subacute thyroiditis [18]. In our patient with the painless form of STLS, a marked rise in serum IL-6 levels was also observed, which persisted even after initiation of prednisone, a phenomenon which was similarly observed in patients with subacute thyroiditis previously reported by Yamada et al. [19]. Acute phase cytokines including IL-6 can be produced by activated leukocytes, fibroblasts or endothelial cells [17]. However, neither inflammatory cell infiltration nor fibrotic change was observed in the amyloid goiter in the present case, even though thyroid was the most suspected focus of systemic inflammation based on the findings of Ga-67 scintigraphy. On the other hand, IL-6 is a cytokine released by the thyrocytes themselves [20, 21] and can be regarded as a marker of thyroid-destructive processes [22]. Therefore, IL-6 produced by damaged thyrocytes potentially due to diffuse amyloid deposition may play an important role in the development of acute severe inflammatory reaction observed in this patient, although the ultimate trigger of such cytokine release by damaged thyrocytes remains to be elucidated.

Among so-called destruction-induced thyrotoxicosis, various disease entities are included in the painful form such as subacute granulomatous thyroiditis, a condition characterized by thyroid swelling exhibiting spontaneous nuchal pain with systemic inflammatory reactions; painful lymphocytic thyroiditis (or acute exacerbation of Hashimoto's thyroiditis); and acute suppurative thyroiditis, although the frequency of the latter two is very rare. On the other hand, the clinically painless form of destruction-induced thyrotoxicosis is almost exclusively restricted to painless or silent thyroiditis, a condition characterized by transient thyrotoxicosis without systemic inflammatory reactions. Histopathologically, painless thyroiditis and painful lymphocytic thyroiditis are indistinguishable forms of lymphocytic thyroiditis (or Hashimoto's thyroiditis), whereas subacute thyroiditis is characterized by granulomatous and giant cell inflammation. Recently painless forms of subacute thyroiditis [23, 24] and acute exacerbation of Hashimoto's thyroiditis [12] were reported. Histopathologically, the former showed classical granulomas with giant cell, while the latter showed typical Hashimoto's thyroiditis. Based on these reports, this patient was first suspected to have painless form of acute exacerbation of Hashimoto's thyroiditis, based on her clinical course which was similar to destruction-induced thyrotoxicosis, and on the positivity of anti-thyroidal autoantibody titers. However, the needle biopsy specimens obtained all showed marked amyloid deposition with no evidence of Hashimoto's thyroiditis. Therefore, since the term 'painless thyroiditis' is a generic one for nontender destruction-induced thyrotoxicosis, we diagnosed this case as painless thyroiditis with severe inflammatory reactions in amyloid goiter.

While the origin of tender thyroid has yet to be elucidated, Furszyfer et al. [25] previously suggested that tenderness is caused by capsular stretching due to acute thyroidal enlargement. In fact the thyroidal size in our patient did not change throughout the observation period, but this is not necessarily the main characteristic of nontender thyroid, since the 6 previously reported cases of STLS [6–10] also noted an almost stable size of goiter, even in remission [9]. In regard to the histopathology of painful lymphocytic thyroiditis, Suzuki et al. [26] and Shigemasa
et al. [27] reported that various histological forms were observed, such as fibrous variant, focal or diffuse lymphocytic thyroiditis. In particular, marked fibrosis with localized edematous inflammation reported by Ishihara et al. [28, 29] and granulocytic infiltration by Suzuki et al. [26], neither of which was observed in the painless form of acute exacerbation of Hashimoto’s thyroiditis [12], may be findings specific to tender thyroid, although the specificity of these findings in painful lymphocytic thyroiditis requires analysis using a larger series of cases. Furthermore, previous reports describing painless subacute thyroiditis [23, 24], including two ‘outbreaks’ of cases [30, 31], do not fully explain the etiology for the condition, except for a report by de Bruin et al. [31] in which the patient exhibited significantly lower frequency of HLA-B35 but increased frequency of HLA-B15 with painless subacute thyroiditis compared with the painful forms. From a diagnostic standpoint, painless thyroidal destruction with definite inflammatory reactions is very difficult to distinguish from etiologies of other fevers of unknown origin such as infections, malignancy and collagen disease, which makes thorough systemic examinations necessary [12, 23, 24]. However, in our case and others [12, 23], intense thyroid uptake of Ga-67 citrate provided the best evidence of the thyroid as the focus.

In summary, to our knowledge this is the first reported case of amyloid goiter with the clinical features of painless thyroiditis accompanied by severe inflammatory reactions. Since the mechanism and etiology of this unusual case remain unclear, the mechanisms causing acute inflammatory changes and tenderness in the thyroid gland should be studied further, focusing on potential inflammatory cytokines and genetic factors including HLA haplotypes.

References

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