Increased pertechnetate and radioiodine uptake in the thyroid gland with subacute thyroiditis and concurrent Graves' disease

Lanzhen Li[1] MD,
Lixia Sun[2] MD,
Shuiqing Yu[3] MD,
Chao Ma[4] MD

1.Department of General Surgery, Linyi People's Hospital, Linyi, Shandong, China
2.Department of Internal Medicine, People's Hospital of Rizhao, Rizhao, Shandong, China
3.Department of Internal Medicine, Linyi People's Hospital of Economic Development Zone, Linyi, Shandong, China
4. Nuclear Medicine, Xinhua Hospital, Affiliated to School of Medicine Shanghai Jiaotong University, Shanghai, China

Keywords: Subacute thyroiditis -Thyroid stimulating hormone receptor antibody -Graves' disease -Pertechnetate scan

Corresponding author:
Shuiqing Yu MD, Woerma Road Economic Development Zone Linyi People's Hospital of Economic Development Zone, Linyi, Shandong, China
Tel: +0539-86--8769222,
yushuiqing126@163.com

Received:
5 January 2016
Accepted revised:
27 January 2016

Abstract

Objective: A 61 years old woman presented with low grade fever and weight loss for a month. Thyroid function tests showed hyperthyroidism: increased technetium-99m pertechnetate ($^{99m}TcO_4^-$) and radioiodine (^{131}I) uptake and elevated thyroid stimulating hormone receptor antibodies (TSHRAb). She also had high erythrocyte sedimentation rate. Fine-needle aspiration (FNA) biopsies of left thyroid lobe revealed subacute thyroiditis (SAT). Simultaneous occurrence of SAT and Graves' disease (GD) was diagnosed. The patient was in good physical condition after two doses of betamethasone and daily administration of low dose antithyroid drugs. **Conclusion:** This case indicated that the measurement of TSHRAb is useful in understanding the clinical course of patients with SAT when thyroid function tests including the ^{99m}Tc and ^{131}I uptake are not compatible with the diagnosis. In such cases, GD should be suspected. The mechanism of high ^{99m}Tc and/or ^{131}I uptake in patients with simultaneous SAT and GD may be due to the inflammatory process which was detected by FNA in a small part of the left thyroid lobe inducing the stimulating effects of elevated TSHRAb on the undamaged follicular cells.

Hell J Nucl Med 2016; 19(1): 49-52 *Epub ahead of print: 1 March 2016* *Published online: 1 April 2016*

Introduction

Subacute thyroiditis (SAT) is considered an inflammatory painful viral infectious disease, frequently accompanied by fever [1]. The diagnosis of SAT is based on typical symptoms and findings, including thyroid pain, fever that can be high, tenderness on palpating the thyroid gland, transient symptoms of thyrotoxicosis, and high erythrocytes sedimentation rate (ESR). The uptake of ^{99m}Tc is markedly decreased [2]. Graves' disease (GD) is an auto-immune disease but there seems to be no relation between the cause of SAT and GD. The possibility of SAT associated with GD is very low. Nevertheless, increased ^{99m}Tc uptake and thyroid stimulating hormone receptor antibodies (TSHRAb) in SAT, and SAT followed by GD have been reported [1, 3-5]. Graves' disease may follow SAT after activation of the autoimmune system responding to the inflammatory nature of SAT in susceptible patients [1]. According to our knowledge, only one case of simultaneous occurrence of GD and SAT has been reported [6]. We here present a rare case of simultaneous occurrence of GD and SAT.

Case Report

A 61 years old woman presented with low grade fever, bad temper and weight loss of 4 kilograms during the last 30 days. She did not complain of neck pain. Physical examination revealed tachycardia, heart rate of 96 beats/minute and a diffusely enlarged thyroid gland without evidence of opthalmopathy. She had mild bilateral fine hands tremor and brisk deep tendon reflexes. Her laboratory values were: TSH 0.01μIU/mL (0.55-4.78), free thyroxine: 39.2pmol/L (11.-22.7), free triiodothyronine (FT3) 11.85pmol/L (3.5-6.5), thyroglobulin (Tg) 279.74ng/mL (1.15-130.77), TgAb17.2U/mL (0-60), thyroperoxidase antibody (TPOAb) <28IU/mL (<60), TRAb 5.51IU/mL (0-1.75), ESR 55mm/h (0-20) and later returned to normal, C-reactive protein 38mg/L (<8), rheumatoid

factor <20IU/mL(0-20) and antistreptolysin O <25IU/mL (0-116). Blood routine tests, renal, and liver function tests were within normal limits. A thyroid ultrasound showed an enlarged heterogeneous and solid tumor (41x21x17mm) in the right thyroid lobe with mild hypervascularity (Figure 1A), multiple small low ECHO areas in the left thyroid lobe (Figure 1B) and enlargement of multiple cervical lymph nodes. Cervical computed tomography (CT) also showed enlarged the right thyroid lobe with decreased density and small nodules with decreased density in the left thyroid lobe (Figure 1C). The 3 and 24 hours uptake after 74kBq of ^{131}I was 26.5% (normal 10%-25%) and 42.2% (normal 15%-35%) respectively. Technetium-99m (^{99m}Tc) thyroid scan showed intensely increased uptake in most parts of the gland, decreased uptake in a small area of the left thyroid lobe, and patchy defects in the right lobe (Figure 2A). Fine-needle aspiration (FNA) biopsy of the left thyroid lobe revealed SAT (Figure 3). These findings led to the diagnosis of both GD and SAT.

Symptoms were well relieved after injecting 2mL of betamethasone (10mg) intramuscularly once a day for two days. Erythrocyte sedimentation rate decreased to 21mm/h a month later. Over the next couple of weeks, her serum T3 and T4 and TSHRAb remained abnormally high with TSH at 0.0018μIU/mL. Antithyroid treatment (ATD) using methimazole from 5-2.5mg was given daily for a total of 21 months. Temporary discontinuation of methimazole induced recurrence of hyperthyroidism. Repeated ultrasound tests revealed diffuse thyroid disease without enlargement of the cervical lymph nodes (Figure 4A and Figure 4B). The repeated ^{99m}Tc thyroid scan 2 years after diagnosis of SAT showed normal radioisotope distribution in both thyroid lobes (Figure 2B). Changes in ESR, thyroid function, Tg and TRAb are shown in Table 1.

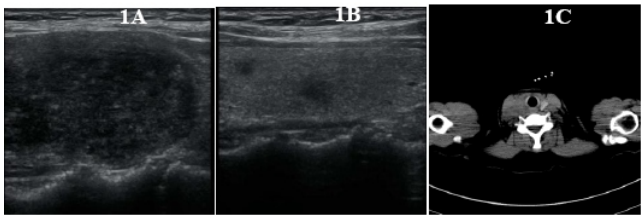

Figure 1. A: Thyroid ultrasound showed an enlarged heterogeneous solid tumor (41x21x17mm) in the right lobe of the gland with mild hypervascularity, and B: with many small low ECHO areas in the left lobe. Cervical CT showed enlarged the right thyroid lobe with decreased density and small nodules with decreased density in the left thyroid lobe both with decreased density (Figure 1C).

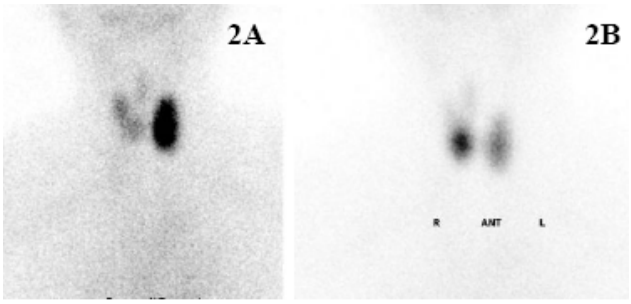

Figure 2. A: ^{99m}Tc thyroid scan showed a intensely increased uptake in most part and decreased uptake in a small area of the left gland, and patchy defects in the right gland. The repeated ^{99m}Tc thyroid scan 2 years after the diagnosis of subacute thyroiditis showed normal radioisotope distribution in bilateral thyroid lobes (B).

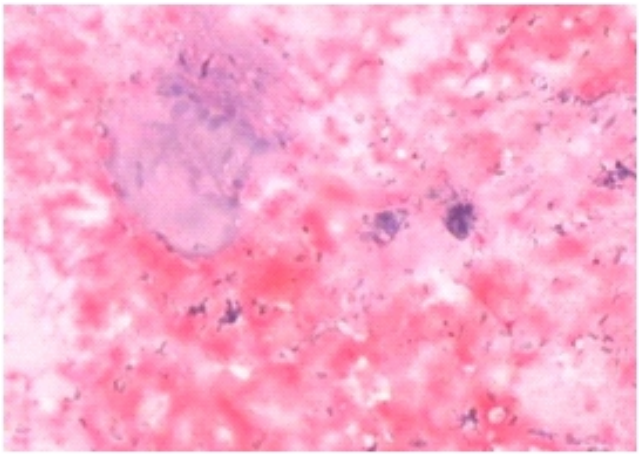

Figure 3. Fine-needle aspiration biopsies of the left thyroid lobe revealed subacute thyroiditis

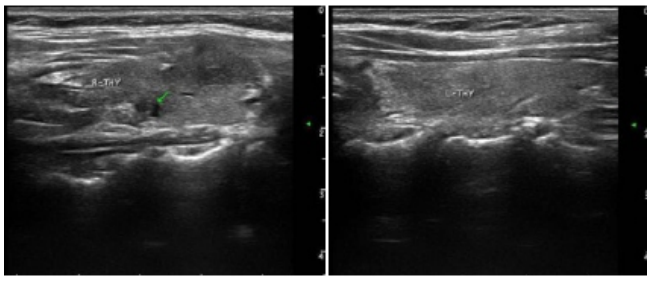

Figure 4. Repeated ultrasound revealed diffuse thyroid disease in the right (A) and the left lobe (B).

Discussion

Subacute thyroiditis is a painful and inflammatory disease frequently accompanied with fever [1] which is consistent with our case. GD is an auto-immune disease. There seemed to be no relation between the causes of the SAT and GD. Simultaneous occurrence of Hashimoto's thyroiditis (HD) and GD, the two main types of autoimmune thyroid disease has been reported [7-10]. These patients had positive TPOAb, while our case had negative TPOAb which ruled out HD. Rare cases of GD occurring years after SAT [4] and SAT after HD [11] have also been reported. We report here a very rare case of simultaneous occurrence of GD and SAT.

The ^{99m}Tc and/or ^{131}I thyroid uptakes were useful to distinguish GD from SAT [12]. Both are usually markedly suppressed in SAT [2, 12] due to the inflammatory process and to the suppressed thyrotropin (TSH). Suppressed TSH is due to the release of thyroid hormone stores [2]. The patchy defects in the right thyroid lobe on the ^{99m}Tc scan corresponded to the diagnosis of SAT. However, ^{99m}Tc and/or ^{131}I thyroid uptake are not always suppressed in SAT [2] as suggested by our case. The first known case of simultaneous occurrence of GD and SAT [6]had heterogeneous trapping of pertechnetate throughout the diffusely enlarged gland with alternative areas of increased and decreased uptake and a relatively low ^{123}I uptake (6.6% at 5 hours with normal

Table 1. *Erythrocyte sedimentation rate (ESR), free thyroxine (FT4), thyroglobulin (Tg) and thyroid stimulating hormone receptor antibody (TRAb) in our patient.*

Dates	ESR values (mm/h)	FT4 values (pmol/L	TSH values (μIU/mL)	TRAb values (IU/mL)	Tg values (ng/mL)
Oct-2013	55	39.2	0.01	5.51	279.74
Nov-2013	21	30.63	0.01	6.81	166.97
Dec-2013	6	20.33	0.018	6.34	
Sep-2014	7	14.37	1.22	1.92	31.93
Oct-2015	4	15.53	0.34	1.03	

4%-15%). Our case had increased both the pertechnetate and the radioiodine uptake in the left thyroidal lobe and also SAT, as confirmed by FNA. It has been reported that some SAT patients have thyroid auto-antibodies [13,14]. The patient responded well to a low dose of ATD (5mg qd). Graves' disease may be suspected when there is a high blood level of TRAb and simultaneously increased ^{131}I uptake. The present case indicated that TRAb was useful in understanding the clinical course of patients with SAT when thyroid function including ^{99m}Tc thyroid scan and ^{131}I uptake tests are not compatible with the diagnosis of SAT.

The presence of auto-thyroid antibodies is transitory, as they disappear several months later, which may be secondary to the release of thyroid antigens [15]. It has been recently reported that TSHRAb were detected 1 year after the diagnosis of SAT, and after 11 years GD with severe ophthalmopathy was diagnosed [16]. Our case had simultaneous occurrence of SAT and GD. It has been reported that TRAb may decrease after prednisolone treatment [3]. Grunenberger et al. (1998) [5] reported a case of GD that relapsed after 5 years. Histology showed evidence of treated GD and signs of SAT in the right thyroid lobe. Our case had positive TRAb even after steroid treatment which returned to normal 1 year after ATD. In SAT, eicosanoids including interleukin-4 (IL-4), prostaglandins and cytokines may be produced in the thyroid [17], and are known to increase TSH-stimulated iodine uptake [17]. Therefore, the mechanism of high ^{99m}Tc and/or ^{131}I uptake may be due to the inflammatory process localized in a small part of the left thyroid lobe as shown by cervical ultrasound and CT. Thereby one may explain the stimulating effects of elevated TRAb on the undamaged follicular cells. Other thyroid radioisotope stimulating factors may also be present. It has been suggested that TSH-induced sodium iodide transport is secondary to Na+-K+ ATPase increase [18, 19], or is mediated by a Na+-dependent iodide transport carrier in the cells membrane [20], and that its effect on TSH is mediated by cyclic adenosine monophosphate [17]. In our case, with resolution of the inflammation and TRAb, both lobes showed homogenous uptake of ^{99m}Tc and TSH and thyroglobulin (Tg) returned to normal.

Mediated genetic susceptibility has been shown in both SAT and GD. Persons with HLA-B35 are susceptible to SAT [21, 22]. A strong linkage between human leukocyte antigen HLA-B35 and SAT has been found in all genetic groups [6, 11, 23, 24], whereas HLA-DRB1 and -DQB1 are consistently associated with GD [25-27]. However, the genetic susceptibility was not tested in our case. Alternatively, the simultaneous presentation of SAT and GD may be coinci-dental [6]. Currently, the paucity of long term evaluations of thyroid antibodies, and nuclear imaging studies in these patients make it difficult to determine the prevalence of simultaneous GD and SAT, or the exact time of the transition from SAT to GD [3, 17].

In conclusion, this case illustrates a rare occurrence of increased pertechnetate and radioiodine uptake in the thyroid gland in SAT and concurrent GD, which needed long term treatment with low dose antithyroid drugs. This case indicated that the measurement of TRAb was useful in understanding the clinical course of SAT because thyroid function tests including ^{99m}Tc thyroid scan and ^{131}I uptake test were not compatible with the diagnosis of SAT with may be due to the inflammatory process localized in a small part of the left thryoid lobe, and also to the stimulating effects of elevated TRAb on the undamaged follicular cells.

The authors declare that they have no conflicts of interest

Bibliography

1. Nakano Y, Kurihara H, Sasaki J. Graves' disease following subacute thyroiditis. *Tohoku J Exp Med* 2011; 225: 301-9.
2. Shigemasa C, Teshima S, Taniguchi S et al. Pertechnetate thyroid uptake is not always suppressed in patients with subacute thyroiditis. *Clin Nucl Med* 1997; 22: 109-14.
3. Fujii S, Miwa U, Seta T et al. Subacute thyroiditis with highly positive thyrotropin receptor antibodies and high thyroidal radioactive iodine uptake. *Intern Med* 2003; 42: 704-9.
4. Bartalena L, Bogazzi F, Pecori F, Martino E. Graves' disease occurring after subacute thyroiditis: report of a case and review of the literature. *Thyroid* 1996; 6: 345-8.
5. Grunenberger F, Chenard MP, Weber JC et al. Relapse of Graves' disease after subacute thyroiditis. *Thyroid* 1998; 8: 683-5.
6. Hoang TD, Mai VQ, Clyde PW, Shakir MK. Simultaneous occurrence of subacute thyroiditis and Graves' disease. *Thyroid* 2011; 21: 1397-400.
7. Majumder A, Sanyal D. A case of simultaneous occurrence of Graves' disease and Hashimoto's thyroiditis. *Indian J Endocrinol Metab* 2012; 16: S338-9.
8. Sutradhar SR, Siddiqui NI, Rahman S et al. Combined occurrence of hyperthyroid Graves' and Hashimoto's thyroiditis. *Mymensingh Med J* 2006; 15: 102-4.
9. Umar H, Muallima N, Adam JM, Sanusi H. Hashimoto's thyroiditis following Graves' disease. *Acta Med Indones* 2010; 42: 31-5.

10. Ohye H, Nishihara E, Sasaki I et al. Four cases of Graves' disease which developed after painful Hashimoto's thyroiditis. *Intern Med* 2006; 45: 385-9.
11. Minciullo PL, Ruggeri RM, Vita G et al. Development of Hashimoto's thyroiditis after subacute thyroiditis: an unusual patient. *Thyroid* 2009; 19: 73-4.
12. Kidokoro-Kunii Y, Emoto N, Cho K, Oikawa S. Analysis of the factors associated with Tc-99m pertechnetate uptake in thyrotoxicosis and graves' disease. *J Nippon Med Sch* 2006; 73: 10-7.
13. Strakosch CR, Joyner D, Wall JR. Thyroid stimulating antibodies in patients with subacute thyroiditis. *J Clin Endocrinol Metab* 1978; 46: 345-8.
14. Tamai H, Nozaki T, Mukuta T et al. The incidence of thyroid stimulating blocking antibodies during the hypothyroid phase in patients with subacute thyroiditis. *J Clin Endocrinol Metab* 1991; 73: 245-50.
15. Iitaka M, Kakinuma S, Yamanaka K et al. Induction of autoimmune hypothyroidism and subsequent hyperthyroidism by TSH receptor antibodies following subacute thyroiditis: a case report. *Endocr J* 2001; 48: 139-42.
16. Hallengren B, Planck T, Asman P, Lantz M. Presence of Thyroid-Stimulating Hormone Receptor Antibodies in a Patient with Subacute Thyroiditis followed by Hypothyroidism and Later Graves' Disease with Ophthalmopathy: A Case Report. *Eur Thyroid J* 2015; 4: 197-200.
17. Weiss SJ, Philp NJ, Ambesi-Impiombato FS, Grollman EF. Thyrotropin-stimulated iodide transport mediated by adenosine 3',5'-monophosphate and dependent on protein synthesis. *Endocrinology* 1984; 114: 1099-107.
18. Wolff J, Maurey JR. Thyroidal iodide transport. II. Comparison with non-thyroid iodide-concentrating tissues. *Biochim Biophys Acta* 1961; 47: 467-74.
19. Wolff J, Halmi NS. Thyroidal iodide transport. V. The role of Na-K-activated, ouabain-sensitive adenosinetriphosphatase activity. *J Biol Chem* 1963; 238: 847-51.
20. Bagchi N, Fawcett DM. Role of sodium ion in active transport of iodide by cultured thyroid cells. *Biochim Biophys Acta* 1973; 318: 235-51.
21. Ishihara T, Mori T, Waseda N et al. Histocompatibility lymphocytic antigen (HLA) typing in patients with acute exacerbation of Hashimoto's thyroiditis. *Endocrinol Jpn* 1988; 35: 231-6.
22. Tamai H, Goto H, Uno H et al. HLA in Japanese patients with subacute (De Quervain's) thyroiditis. *Tissue Antigens* 1984; 24: 58-9.
23. Rubin RA, Guay AT. Susceptibility to subacute thyroiditis is genetically influenced: familial occurrence in identical twins. *Thyroid* 1991; 1: 157-61.
24. Kramer AB, Roozendaal C, Dullaart RP. Familial occurrence of subacute thyroiditis associated with human leukocyte antigen-B35. *Thyroid* 2004; 14: 544-7.
25. Simmonds MJ, Howson JM, Heward JM et al. Regression mapping of association between the human leukocyte antigen region and Graves disease. *Am J Hum Genet* 2005; 76: 157-63.
26. Park MH, Park YJ, Song EY et al. Association of HLA-DR and -DQ genes with Graves disease in Koreans. *Hum Immunol* 2005; 66: 741-7.
27. Ramos-Lopez E, Fernandez-Balsells M, Kahles H et al. HLA-DQ haplotypes in Spanish and German families with Graves' disease: contribution to DQA1*0501-DQB1*0301 mediated genetic susceptibility from fathers. *Thyroid* 2007; 17: 1131-5.

Alberobello, a UNESCO World Heritage Site, Province of Bari, Italy.