# Family Practice Grand Rounds

# The Deceptively Tender Goiter

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DR. T. EUGENE TEMPLE, JR *(Director of Medical Education, Riverside Hospital):* Grand Rounds today concentrates on the multiple problems of a patient followed for the last two years with an enlarged tender thyroid gland. The objectives for this session are: (1) to consider the clinical and laboratory features of this case of thyroiditis; (2) to analyze each stage of this patient's illness as related to these clinical/laboratory features; and (3) to review the several therapeutic maneuvers used in this patient. From this patient's story you should identify the reasons why patients with thyroid disease require prolonged, careful follow-up. Dr. Gordon Wilhoit will present the case.

DR. GORDON WILHOIT *(Chief Resident, Family Practice Center)*: This 29-year-old married caucasian female, mother of four small children, presented with the complaint of pain in her neck and throat of two weeks' duration. She had been healthy following the birth of her youngest child 18 months before this visit. Her children and husband had been well. She had felt tired for several weeks but considered this to be part of the multiple demands on her as a wife and mother of young children. She denied any fever or recent weight change and was not taking any medications. Review of systemic complaints was unhelpful. Specifically, she denied any rapid heart beat, palpitations, shortness of breath, weakness, appetite or bowel change. Her menstrual history was normal. The past history revealed four routine pregnancies with uncomplicated vaginal deliveries. As a young child, she underwent a tonsillectomy and adenoidectomy. She had no allergies or drug sensitivities. Family history indicated that her mother had a thyroid condition, and she recalled that her maternal grandmother had a fairly large goiter which was never treated. Social history was unhelpful.

Physical examination revealed an afebrile, well-developed, well nourished, white female, weighing 122 pounds with height of 5 feet 3 inches. She had moderate discomfort, aggravated by swallowing. Her blood pressure was 115/80 mmHg and pulse rate, 88 beats per minute. Her head, eyes, ears, nose, and throat were normal. The neck was

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supple to movement, but she experienced moderate discomfort with flexion. The thyroid was diffusely enlarged to an estimated weight of 75 gm, approximately five times normal size, and was quite tender. The jugular venous pulses were normal. No lymphadenopathy was detected. Her chest was symmetrical and moved equally and normally with respiration. The breast examination was normal. Cardiac examination revealed a regular rhythm, rate of 88 beats/min (sitting) and 80 beats/min (supine). The sounds were normal and no murmurs, gallops, or rubs were heard. Abdominal, pelvic, rectal, spine, extremity, and neurological examinations were normal.

Our clinical diagnosis at this time was subacute thyroiditis. Dr. Williams saw the patient with me in the center. Would you comment on your initial assessment of this patient?

DR. ROBERT B. WILLIAMS *(Assistant Director of Family Practice Center)*: The diagnosis appeared straightforward at this initial visit. On observation of the anterior neck area, the enlarged gland was readily evident, and one could see a slight redness of the skin covering it. It was indeed very tender to palpation. The patient winced during examination. It was diffusely enlarged with no palpable nodules.

DR. WILHOIT: Treatment was initiated with aspirin and L-thyroxine, 0.15 mg orally each day. The patient returned to the office three weeks later, improved symptomatically, but the thyroid gland remained approximately the same size. Treatment was continued.

DR. GEORGE S. MITCHELL, JR *(Director of Family Practice Center):* You did not report any laboratory data at the first visit. I realize that in such a clearcut situation one may question the need for expenditure of money for laboratory work if it isn't going to enhance the diagnosis and/or treatment. I would be interested in her erythrocyte sedimentation rate (ESR) and serum thyroxine.

DR. WILHOIT: The serum thyroxine was 10.8 μg/100 ml (normal range 4.8 to 12.8 μg/100 ml) and the sedimentation rate was 46 mm/hour (Wintrobe method). This is consistent with the clinical diagnosis, though I would not have been surprised to find the ESR even higher, up to 80 to 100 mm/hour.

DR. SUSAN SATCHWELL *(Assistant Director of Family Practice Center)*: Did you obtain a radioactive iodine uptake study? I would expect it to be low.

DR. WILHOIT: No, we did not, but, as you will see later, this was probably an error since it might have helped to clarify her subsequent course of events. However, I did not believe it would be of help at this time in our management program and, frankly, tried to save her money. This patient was presented at the Endocrine Consultant Conference, and I have asked Dr. Temple to make a few comments about his assessment of her and subacute thyroiditis in general.

DR. TEMPLE: By the time I examined this patient, she had recovered partially. From the above description, I concurred with the diagnosis of subacute thyroiditis. The only moderately elevated ESR did concern me since striking elevations are usually found in this disorder.[1] Actually this ESR was a clue to the correct diagnosis, but the history and examination are so typical of subacute thyroiditis that I suppressed the ESR information as misleading diagnostically. Another important negative fact in this patient is the absence of any fever. Most patients with subacute thyroiditis have at least minimal elevation of temperature, ie, up to 100-101 F orally, during the initial phase of the illness. In addition, they complain of pain radiating to the ears and, occasionally, to the lower facial region. I have seen three people with this disorder whose presenting complaint was earache, and one in whom I considered maxillary sinusitis prior to neck palpation. In the past, many such patients appeared quite ill when first seen, but in the last decade, I have seen many who resembled the present patient. One minor point relates to her diffuse goiter. In the older literature it is more common to find one thyroid lobe enlarged more than the other, though diffuse, symmetrically enlarged glands are described.[1] Also, mild cases, which run a chronic course, (many months to years) have been reported. In these latter cases, fever, pain, and even thyroid tenderness may be absent. Fortunately, subacute thyroiditis is most often a self-limited benign disease.

In considering the inflamed goiter, one must recall several potential diseases and also several etiologic mechanisms. I use the simple classification shown in Table 1. From this approach, let me admit quickly that I've seen only one patient with the acute-suppurative type. While that patient's illness was acute and devastating, it must be a rare

| Table 1. Classification of Thyroiditis | |
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| **Type** | **Mechanism** |
| 1. Acute | Bacterial |
| 2. Subacute | Viral |
| 3. Chronic | Autoimmune |
| 4. Riedel's | Unknown |

disease now. It bothers me to classify thyroiditis this way because subacute thyroiditis may be equally as acute as the first type, though the etiologies are different. Subacute thyroiditis may present with an exquisitely tender and painful thyroid gland, appearing rather fast, but the temperature is less elevated than in the bacterial variety associated with temperatures of 104 F orally, or higher. Staphylococcus aureus is the most frequent organism associated with suppurative thyroiditis.[1] My one patient had Salmonella Type B and also had sickle cell disease (Hemoglobin SS). In contrast, the etiology in subacute thyroiditis is generally considered to be viral. Volpe et al have found significant titers of antibodies to influenza, adenovirus, mumps, and Coxsackie and Echo viruses.[2] These titers disappear from the serum at intervals of 16 to 40 weeks which is not too far off the clinical course of the average patient at two to five months.

Treatment of the patient with mild to moderate symptoms is exactly what Dr. Wilhoit described, ie, aspirin and L-thyroxine. In more severe cases, one may wish to use glucocorticoids. I usually prescribe prednisone starting at a dose of 40 mg orally each day and tapering rapidly over seven to ten days to nothing but, as has been reported previously, relapse is not uncommon after use of glucocorticoids, necessitating re-treatment.[3] I cannot confirm that suppressing pituitary TSH (thyroid stimulating hormone) with L-thyroxine does any good for these patients. Teleologically, it makes sense, except in those few patients who develop hyperthyroidism with subacute thyroiditis.[3] In the past, a few people have actually stimulated the thyroid by TSH administration. This has never seemed reasonable to me since the gland is quite disrupted histologically. It has not been proved to be effective.[1] After several weeks to several months of subacute thyroiditis, the patient's initially normal or slightly elevated plasma $T_4$ and $T_3$ levels may become subnormal. This reflects depletion of the thyroid follicles of stored hormone. The serum TSH does rise and symptomatic hypothyroidism may be evident on clinical examination. It is reasonable to give L-thyroxine at this time, if it has not been prescribed before. However, one should watch for complete subsidence of thyromegaly and thyroid tenderness and should discontinue L-thyroxine at that time. Only rarely have cases of subacute thyroiditis been reported to leave permanent thyroid damage with persisting hypothyroidism.[1,3] I have never seen a patient develop this. On the other hand, an additional pertinent comment about the etiology of subacute thyroiditis relates to possible autoimmune disease as a cause. We see far more autoimmune thyroiditis, labeled Hashimoto's disease, than we do the subacute variety. One may find positive antithyroglobulin and antimicrosomal antibody titers in subacute thyroiditis just as one finds in many cases of Hashimoto's disease and, also, in Graves' disease.[4] However, the titer is lower in subacute thyroiditis, ie, often less than 1:1000, while, at least in Hashimoto's disease, the titers are usually in the thousands, not infrequently greater than 1:20,000. Thus, autoimmunity does not appear to be an etiologic factor in subacute thyroiditis.[1,2,4] Rather, the autoantibodies appear to reflect secondary release of antigenic material from the disrupted thyroid.[1,4] Dr. Harrington will present the next portion of this patient's illness.

DR. WILLIAM HARRINGTON *(Chief Resident in Family Practice for Riverside Hospital)*: This 30-year-old white female appeared in my office some eight months after her visit to my partner, Dr. Wilhoit, who was away at the time.

Her previous illness had disappeared after three months, but about six weeks before this visit, she noted onset of heart palpitations and pounding at night, sweating almost constantly through the day and night, an increased appetite, but a weight loss of six to eight lbs. She was taking nothing though she had been dieting for several months following an eight to ten pound weight gain after her last illness. The remainder of her history was unchanged.

Physical examination revealed a weight of 119 lbs, blood pressure, 145/75 mmHg in right arm (sitting). Pulse of 110 beats/min and regular. She appeared agitated. The thyroid was diffusely enlarged, very slightly tender, and moved freely. I estimated the weight of the gland at 90 gm, about six times larger than normal. The carotid pulses were bounding but I heard no bruits. She showed mild generalized lymphadenopathy. Her heart rate was 110 beats/min (sitting and supine). There was a grade 3/6 systolic ejection murmur audible over the pulmonic area. Her lungs were clear, but respiratory rate (supine) was 25/min. Her muscle strength was good, but she fatigued rapidly with deep knee bends. Her reflexes were 4+ active and symmetrical and the reflexes relaxed rapidly.

My diagnosis was hyperthyroidism, but at this visit, I could not be certain whether this resulted from subacute thyroiditis, as mentioned before, or from Graves' disease. Dr. Spence saw the patient with me.

DR. STEVEN SPENCE *(Assistant Director of Family Practice Center)*: I concurred in the diagnosis of hyperthyroidism. To confirm the diagnosis, we obtained a serum $T_4$ and $T_3$ resin test but, as this should be elevated from either of these causes of hyperthyroidism, we scheduled her for radioactive iodine (RAI) uptake study at the hospital. This should separate the two diagnostic considerations since the RAI uptake would be elevated in Graves' disease and low in the hyperthyroidism of subacute thyroiditis.

DR. HARRINGTON: Her serum $T_4$ was 14.9 $\mu$g/100 ml and $T_3$ resin 38 percent. The RAI uptake was 39 percent at 24 hours (normal range 6 to 33 percent for this laboratory).

DR. SPENCE: With these results, Dr. Harrington and I felt fairly confident in proceeding with antithyroid drug therapy for Graves' disease. The history of thyroiditis some months before concerned us and, therefore, we did not wish to make an irreversible therapeutic decision. We started treatment with propylthiouracil, 100 mg orally every six hours. At the visit before the RAI study, we had prescribed propranolol, 20 mg four times a day, to control her hyperkinetic state. This gave good symptomatic response.

DR. HARRINGTON: The patient was seen in follow-up two months later. Two weeks before this visit she had reduced the dose of propranolol sequentially over a four-day period to none. Symptomatically and objectively she was well controlled at this visit. Her pulse rate was 74 beats/min and blood pressure, again, 158/80 mmHg. The thyroid, however, remained the same size as when first seen. The cardiac and neurological examinations were now normal. Dr. Spence and I consulted and decided to continue the propylthiouracil and to discuss her case with everyone at the next Endocrine Consultation Conference. Prior to this, I talked with Dr. Temple by telephone and received the suggestion to perform thyroid antibody tests before the conference. The serum thyroglobulin (Tg) antibody was negative, but the serum thyroid microsomal antibody was positive at 1:32,000 titer.

DR. TEMPLE: Seeing this patient for the second time for thyroid dysfunction in one year triggered several thoughts. Most of us try to find a common denominator for the multiple manifestations of any illness, particularly in a young person. Why concern ourselves with several diseases when one will do? In this patient, it seemed reasonable to consider one etiology to explain both thyroid illnesses. Autoimmune disease appeared highly likely and from that arose my suggestion to measure thyroid antibodies. I asked Dr. Wilhoit, who was an endocrine elector with me that month, to review autoimmune thyroid disease, and he will present some information that may explain this patient's situation.

DR. WILHOIT: In reviewing this subject, one finds, as usual, that diagnostic testing for thyroid antibodies is not as reliable as one would like. First, there is general acceptance that both Graves' disease and Hashimoto's disease result from autoimmune disease.[4] If one tests slices of thyroid tissue with a serum containing thyroglobulin and/or thyroid microsomal antibodies, immunofluorescence can be demonstrated with the microsomal antibody in sections of thyrotoxic

human thyroid.[4,5] In many patients, the Tg antibody will also produce fluorescence even with non-thyrotoxic and non-Hashimoto thyroid slices. For practical clinical assay for these antibodies, hemagglutination and complement fixation (CF) tests are most often used. However, only about 60 percent of patients with Hashimoto's disease have titers greater than 1:10 for Tg antibodies using hemagglutination, and only 80 percent for the antimicrosomal antibodies. Using the CF assay, one detects a significant titer of antimicrosomal antibodies in only 50 percent of cases. These antibodies are found with similar frequency in Graves' disease patients using these assay methods. Thus, the distinctly positive antimicrosomal antibody in this patient does not help us separate whether she has hyperthyroidism due to Graves' disease or associated with Hashimoto's thyroiditis.

Secondly, we wondered about studying her for thyroid stimulating immunoglobulins (TSI). The most well known of these is long acting thyroid stimulator (LATS) which was first described by Adams and Purves in 1956.[4] LATS testing is not generally available but LATS has been identified in patients with Hashimoto's disease, as well as in those with Graves' disease and in some normal people.[4,6] Consequently, in recent years, significant question has arisen as to its pathogenic role in Graves' disease. Identified, but as yet of research interest, are human TSIs, LATS-protector, another IgG antibody, and anti-TSH receptor antibodies.[4] Thus, we could not turn to any of these assays for clinical aid.

Finally, after considering all of the information about autoimmune thyroid disease, one returns to further clinical testing of the patient to try to distinguish between these two autoimmune entities. First, we considered a $T_3$ suppression test of RAI uptake, but neither Graves' disease nor Hashitoxicosis cases are normally suppressible with $T_3$ administration.[4] Next, we asked ourselves about the biological activity of this patient's gland. We had already assessed the functional activity with the serum $T_4$ and $T_3$ and the RAI uptake. A scan might be of use as patients with Graves' disease show an intense uptake of isotope throughout the gland while those with Hashimoto's disease exhibit a somewhat patchy uptake with variable areas of relative inactivity throughout the gland.[1,3,4] In this patient, we observed a patchy-spotted pattern of isotope accumulation more like that seen in Hashimoto's disease. Therefore, our clinical diagnosis was Hashimoto's thyroiditis with hyperthyroidism.

DR. TEMPLE: In addition to this finding which suggests Hashimoto's disease as the basic lesion, from anecdotal evidence, I believe that the titer of antimicrosomal antibodies is more consistent with Hashimoto's thyroiditis than with Graves' disease. While I find titers of 1:1600 in Graves' disease patients not uncommonly, a titer such as that found in this patient is rare, except in patients with Hashimoto's thyroiditis. In fact, in reviewing my own series of Graves' disease patients, in whom I've obtained this assay, in practically all, I could not find one with a titer of this magnitude.

DR. MITCHELL: What about long-term management of this patient? Should she have definitive therapy with I-131 or a subtotal surgical thyroidectomy or continue with propylthiouracil (PTU)?

DR. HARRINGTON: This was considered in detail at the Consultant Conference. It was left with Dr. Wilhoit and me to discuss the decision with the patient. Our approach was to give her all three alternatives after explaining the potential risks and benefits of each modality. However, we recommended, after full discussion, that she continue with propylthiouracil, to which she agreed. This recommendation arose from the observation that Hashitoxicosis (combined Hashimoto's thyroiditis and hyperthyroidism) usually subsides after a few months to a year and it is not uncommon for the patient to progress to hypothyroidism.[3,4]

DR. SATCHWELL: I believe there has been a reported increased incidence of thyroid cancer with Hashimoto's thyroiditis, at least from some centers.[7] Are you concerned about that since no biopsy has been obtained and medical therapy has been continued?

DR. TEMPLE: First, I agreed totally with the decision to treat with PTU. Secondly, I believe the incidence of thyroid carcinoma has been overemphasized in patients with Hashimoto's disease and, to a lesser extent, in Graves' disease. In fact, Doniach and others[1,5] have noted areas of lymphocytic thyroiditis adjacent to thyroid carcinomas. This may represent an immune reaction of the gland against the carcinoma rather than development of carcinoma in association with autoimmune thyroiditis. Thirdly, the advantage of primary care over tertiary care is that the patient

will return to see the primary physician regularly. Therefore, in this patient, her physician can evaluate her goiter over time. If she develops the expected lobulated, slightly nodular goiter with serrated borders which is seen in Hashimoto's disease, one can be fairly certain that she is following the predictable course of this disease. On the other hand, if she develops a large nodule, distinct from the remainder of the gland, then further study and consideration of a biopsy might be recommended. If such a circumstance appears, my recommendation would be open surgical biopsy because closed needle biopsies of the thyroid may miss the suspected lesion. I have been guilty of missing thyroid cancer using this method. The surgeon has the advantage of getting a wider biopsy and having a frozen section histologic examination done, before doing more surgery. Finally, it has been well established that in areas of nonendemic (iodine deficiency) goiter, the most common cause of moderate sized, nontoxic goiter is Hashimoto's disease.[1,3,4]

The main problem to watch for in this patient, after subsidence of the hyperthyroid state, is the development of hypothyroidism.[3,8] The best test for this, if clinical suspicion suggests it, is a plasma TSH assay. Another factor in her situation that suggests Hashitoxicosis is how quickly and easily her hyperthyroidism was controlled by only moderate doses of PTU. I would follow her with the expectation that hypothyroidism will develop, though total remission of Hashimoto's disease to a euthyroid state has been reported.[1]

DR. MITCHELL: One final question. Dr. Wilhoit, should we be concerned about any other autoimmune disorders in this patient, either now or that may develop in the future?

DR. WILHOIT: There are many potentially associated diseases. The classic example is Schmidt's syndrome: the triad of lymphocytic thyroiditis lymphocytic adrenalitis, and diabetes mellitus.[9] In addition, associations with adrenal insufficiency, hypoparathyroidism, pernicious anemia, and hypogonadism have been reported as isolated as well as combined phenomena.[10] Thyroid autoantibodies have been identified in the sera of such patients. The association with other supposed autoallergic diseases such as systemic lupus erythematosus, rheumatoid arthritis, acquired hemolytic anemia, and Sjögren's syndrome are less well substantiated.[1] Of these, an association with rheumatoid arthritis is most frequently recognized.[11]

DR. MITCHELL: Thank you. It appears from this discussion that long-term careful clinical follow-up is needed for this patient. It indicates also that "all that glitters isn't gold." She may well have had the uncommon appearance of Hashimoto's disease presenting as subacute thyroiditis, resolving temporarily with minimal intervention, and then reappearing as another uncommon presentation with Hashitoxicosis.[1,3,12]

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