Lymphocytic (Auto-immune, Hashimoto's) Thyroiditis

Presentation of an Unusual Case with Subacute Onset in a 14-year-old Girl

JAMES R. HUMBERT, RONALD W. GOTLIN, GLENN HOSTETTER,
JOHN G. SHERRILL, and HENRY K. SILVER

From the Department of Pediatrics, University of Colorado School of Medicine, Denver, U.S.A.

Lymphocytic (auto-immune, Hashimoto's) thyroiditis was formerly considered to be a rare condition in childhood, but recent reports indicate that it is by no means uncommon in this period of life and that it is being recognized with apparent increasing frequency (Macksood, Rapport, and Hodges, 1961). Since Hashimoto wrote his historical paper on struma lymphomatosa in 1912, 247 cases of proven Hashimoto's thyroiditis in children have been reported (Table I).

There has been no explanation for the apparent increased incidence of lymphocytic thyroiditis in all parts of the world, but it may have resulted in part from an increased awareness of the disorder rather than a true increase in its frequency. At the present time lymphocytic thyroiditis appears to be the most common cause of goitre in childhood, comprising about two-fifths of all non-toxic goitres and approximately one-fifth of all goitres seen by physicians (Saxena and Crawford, 1962).

This paper presents an unusual case of lymphocytic thyroiditis in a 14-year-old girl, and discusses the salient features of this condition as compiled from a review of the world literature.

Case Report

The patient was a Caucasian girl who had been well until the age of 14 years, 8 months before admission, when she began to have painless swelling of the anterior portion of the neck, menstrual irregularities, irritability, nervousness, and epigastric and substernal pain. About 4 months later, the neck swelling became more noticeable and exquisite tenderness developed. Pressure symptoms, including dysphagia, dysarthria, and dyspnoea, appeared. She remained afebrile, and received no specific treatment.

Two years previously, she had had an episode of

jaundice, nausea, and vomiting. Subsequently, she had had a series of convulsions for which she had received trimethadione. There was no family history of thyroid disease or any 'auto-immune' disorder.

At the time of admission to hospital, the temperature was (36° C.), pulse 88, and blood pressure 104/72 mm. Hg. She had difficulty in speaking, and held her head in a rigid position because of extreme pain in the anterior portion of the neck. She appeared slightly myxoedematous, with dry skin; the hair was of normal texture. The thyroid gland was much enlarged, moderately firm, and slightly nodular; no bruit could be heard over it. The entire gland was exquisitely tender to the lightest touch and painful on minimal movement; pain was referred to the angle of the jaw and into the ear. There was no lymphadenopathy or hepatosplenomegaly. Neurological examination was negative and the remainder of the physical examination was within normal limits.

Laboratory data. Complete blood count was normal; Hb 13.2 g./100 ml. and WBC, 6500. BUN was 17 mg./100 ml.; fasting blood sugar, 85 mg./100 ml.; alkaline phosphatase, 2.3 King-Armstrong units; SGOT, 16 units. Initially the total bilirubin was 2.9 mg./100 ml.; one week later it was 0.6 mg./100 ml. ESR 49; rheumatoid arthritis latex fixation test, positive; VDRL, negative; lupus erythematosus (LE) preparation, negative on three occasions; cold agglutinins, negative; direct Coombs reaction, positive; indirect Coombs reaction, negative; total protein, 8.6 g./100 ml.; serum protein electrophoresis: albumin 3.1, α_1 -globulin 0.3, α_2 -globulin 1.0, β -globulin 0.9, and γ -globulin 3.3 g./100 ml. Immunoglobulins subsequently were: γ_0 -globulin 1476 (normal = 1248 $\pm$ 221), γ_1 -globulin 342 (normal = 168 $\pm$ 54), and γ_2 -globulin 255 mg./100 ml. (normal = 96 $\pm$ 31).

The T_3 test was 17% (normal = 23–33%); PBI, 1.9 mg./100 ml.; cholesterol, 200 mg./100 ml.; radioactive iodine uptake, 1% at 6 hours, and 6% at 24 hours. The thyroid scan after the administration of radioactive iodine showed diffuse hypoconcentration. The titre

TABLE I
Reported Cases of Lymphocytic Thyroiditis in Childhood—Selected Findings

Reference	No. of Cases	Age (yr.)	Sex	Duration of Goitre (yr.)	Pain	Pathological Findings	Laboratory Findings	Family History
McGuillan (1938)	1	14	F	2	Not mentioned	Typical Hashimoto, with small amount of fibrous stroma		1 sister with goitre
Bogart (1938)	1	14	F	2	None	Early Hashimoto		
Hellwig (1938)	1	16	F		None	Typical Hashimoto with thyroid tissue divided into lobules by fibrous trabeculae of variable thickness		
Joll (1939)	1	10	F		None	Typical Hashimoto with diffuse infiltrative fibrosis		
Schilling (1945)	1	15	F	3/12	Occasional sharp pain to rt. ear and neck	Typical Hashimoto with slight interlobular increase in connective tissue		
Parmley and Hellwig (1946)	2	16	F	1	Not mentioned	Both typical Hashimoto		
Lasser and Grayzel (1949)	1	7½	F	20 1½	Not mentioned	Typical Hashimoto	Chol., 233 mg./100 ml.; BMR, -8%	
Davison and Letton (1949)	1	14	F		None	Acidophilic degeneration of thyroid epithelium with replacement by lymphoid and fibrous tissue		
Statland, Wasserman, and Vickery (1951)	2	10 14	F F	4 2	Mild tenderness in some patients	Typical Hashimoto	Chol., 14-326 mg./100 ml.; BMR, +16 to -33%; PBI, 0.9-4.4 µg./100 ml.; RAI, 15.6-58% (48 hr.)	
Gribetz <i>et al.</i> (1954)	6	9½-13	F	3½-7	None	Typical Hashimoto	PBI, 0.9-8.8 µg./100 ml.; BEI, 3.7-5.6 µg./100 ml.; RAI, 25-84%	
Marshall and Meissner (1955)	1	15	F		Pain rarely recorded, tenderness rarely noted	Typical Hashimoto, at times accompanied by mild fibrosis		
Lindsay, Dailey, Friedlander, Yee, and Soley (1952)	25 1	10-20 <10	F F		Not mentioned	Large series of Hashimoto, mostly adults with all stages of evolution, from eosinophilic degeneration of epithelium to keloid pattern		
Norris and Pollock (1955)	2	7 10	F F		None	Typical Hashimoto		
Davis and Hanske (1955)	1	11	F		None	Typical Hashimoto	PBI, 7.8 µg./100 ml.; BMR, -24%; BP, 84/40 mm. Hg	

continued

TABLE I—continued

Reference	No. of Cases	Age (yr.)	Sex	Duration of Goitre (yr.)	Pain	Pathological Findings	Laboratory Findings	Family History
Skellern, Crile, McCullaugh, Hazard, Lewis, and Brown (1956)	1	12	F	2	Not mentioned	Typical Hashimoto	BMR, -25%; PBI, 5.1 µg./100 ml.; BEI, 2.5 µg./100 ml.; RAI, 78%; γ-glob., 1.18 g./100 ml.	
Ricca, Morriore, and Adel (1956)	1	13	M	8	None	Typical Hashimoto	ESR, 5 mm.; Chol., 212 mg./100 ml.; RAI, 28.1%	
Owen and McConahey (1956)	2	9 17	F F		Not mentioned	Typical Hashimoto	PBI, 3.1 µg./100 ml.; PBI, 5.6 µg./100 ml.	
Lyday (1957)	1	9	F		None	Typical Hashimoto with some fibrous thickening of stroma	PBI, 4.1 µg./100 ml. (post-op.); Chol., 160 mg./100 ml.	
Buxton (1957)	2	15	F		Not mentioned	Lymphocytic thyroiditis		
Frid and Wijnblad (1957)	1	8	F		Not mentioned	Not mentioned		
Hendrick (1957)	1	8	F		Not mentioned	Adenoma removed 2 yr. before; recurrence of goitre, re-op.; micro: early Hashimoto, accompanied by adenocarcinoma		
Wilkins (1957)	3	18 and less	F		Not mentioned	Typical Hashimoto		
Farber and Craig (1958)	1	15	F	3½	Mild discomfort of anterior neck radiating to ear			
Dunning (1959)	3	14 18 19	F F F	1 9 3	None	Typical Hashimoto		
Brown and McGarity (1959)	1	11	F		None	Typical Hashimoto with some areas of atrophy and of fibrous tissue	PBI, 3.8 µg./100 ml.; BMR, -15%; RAI, 8.5%	
Woolner, McConahey, and Beahrs (1959)	8	0-9:2 10-20:6	F F		None	Typical Hashimoto		
Berglund, Broberger, and Zetterström (1960)	5	5, 8, 9, 12, 12,	3F 2M		None	Hashimoto with some increase in connective tissue (1 case, 8-year old boy)		
Clayton and Johnson (1960)	12	6½ to 14	F		None	Typical early Hashimoto	PBI, 4.5-8.8 µg./100 ml.; BEI, 2.9-5.3 µg./100 ml.; RAI, 7.6-42%	2 family histories of thyroid disease
Doniach <i>et al.</i> (1960)		18	F	2	Rapid, painful thyroid swelling	Active advanced lymphadenoid process	PBI, 10 µg./100 ml.; RAI, 1% (24 hr.); γ-glob., normal; Le prep., negative; T-ab: CFT titre, 512; TRC, negative	
Schlicke, Hill, and Schultz (1960)	12	10-20	F		Not mentioned	Hashimoto		
Shands (1960)	1	9	F	1	Not mentioned	Hashimoto without oxyphilic changes		

continued

TABLE I—continued

Reference	No. of Cases	Age (yr.)	Sex	Duration of Goitre (yr.)	Pain	Pathological Findings	Laboratory Findings	Family History
Chimenes, Klotz, and Sors (1961)	1	20	F	10	None	Typical Hashimoto	γ -glob., normal; T-ab, negative; Coons fluorescent ab, + + +; ESR, 3-7 mm.	
Paris, McConahey, Tauxe, Woolner, and Bahn (1961)	1	13	F	2	Not mentioned	Not mentioned	PBI, 7.0 μ g./100 ml.; RAI, 26% (24 hr.)	
Farber and Vawter (1961)	1	11	M		None	Typical Hashimoto	PBI, 5.3 μ g./100 ml.; BEI, 5.2 μ g./100 ml.; T-ab, 1:320	
Macksood <i>et al.</i> (1961)	2	5 8	F F		None	Hashimoto	Increased α_1 , α_2 , and γ -glob.; more or less decreased β -glob.	
Saxena and Crawford (1962)	32	2-15	29F 3M		2 with pain	Typical Hashimoto	PBI, 2-10.2 μ g./100 ml.; BEI, 1.1-5.1 μ g./100 ml.; ab, 0-+ + +; RAI, 24-85%	
Van Wyk, Wynn, Deiss, Arnold, and Graham (1962)	2	15 12½	F F	3 4/12		Hashimoto	Cephalin chol., + + +; haemagglutination and CFT-ab, + + +; RAI, 40% (24 hr.)	Family of 381 members (7 generations) showed evidence of dominant transmission of auto-immune thyroid disorder
De Groot, Hall, McDermott, and Davis (1962)	1	12	F		None	Typical Hashimoto		
Buffat (1963)	1	30	F	13	Not mentioned	Hashimoto's thyroidosis		
Houston and Shee (1963)	1	19	F		Not mentioned	Not mentioned		
Hung and Winship (1963)	1	6½	F		Not mentioned	Hashimoto with slight fibrosis	ESR, 10 mm.; γ -glob., 1.6 g./100 ml.; LE prep., negative; RAI, 63% (4 hr.), 70% (24 hr.)	Mother, Hashimoto; 2 of 3 sibs with 1+ and 4+ Coons fluorescent ab; father neg. for ab
Zaino and Guerra (1964)	2	22 22	F F	6 8	Not mentioned	Typical Hashimoto	Latex test for thyroglob. auto-precipitin slightly +	Identical twins
Jubin, Schmid, and Berchtold (1964)	1	19	F	Few months	None	Typical Hashimoto	ESR, raised; chol., 180 mg./100 ml.; BMR, -11%; PBI, 2.7-4.6 μ g./100 ml.; γ -glob., 1.96 g./100 ml.; T-ab latex +; thyroglobulin-ab, pos. at 1:25; CFT-ab, neg.	
Nilsson and Doniach (1964)	35	7-17	29F 6M		3 with pain	Not mentioned	BMR, -38 to +18%; γ -glob., 1.7 to 2.2 g./100 ml.; T-ab, + to + + + +; PB ¹³¹ I, 0.15 to 1.71 (48 hr.); ESR, 10-25 mm.	See Doniach <i>et al.</i> (1965)

continued

TABLE I—continued

Reference	No. of Cases	Age (yr.)	Sex	Duration of Goitre (yr.)	Pain	Pathological Findings	Laboratory Findings	Family History
Leboeuf and Bongiovanni (1964)	31	8½–10½	26F 5M		Not mentioned	Typical Hashimoto with minimal fibrosis	γ-glob., 1·16 to 1·39 g./100 ml.; T-ab, high; RAI (24 hr.): 5 cases, <20%, 12 cases, 20–45%, 5 cases, >45%	
Becker, Titus, Woolner, and McConahey (1965)	1	8	F		Not mentioned	Hashimoto		
Klein (1965)	1	6	F		Not mentioned	Not mentioned		
Hahn <i>et al.</i> (1965)	27	8–14	F F		1 with sub-acute onset	Typical Hashimoto	γ-glob., normal; discrepancy PBI–BEI, more than 1 μg./100 ml.	One family with 2 sisters and father, Hashimoto; 9 other family histories of non-toxic goitre, exophthalmic goitre, myxoedema, or SLE
Doniach <i>et al.</i> (1965)	38*	2 1	F M		Not mentioned	Not mentioned	T-ab all positive; parietal cell ab, 18% +; anti-nuclear factor, 28% +	64% of mothers with T-ab, 32% with gastric ab; thyroid or auto-immune history in 34 of 37 families
Brecher, Hirsch, and Gould (1965)	1	17		1	Not mentioned	Lymphocytic goitre		
Wolfson and Kahana (1965)	1							

PBI, protein bound iodine; BEI, butanol extractable iodine; BMR, basal metabolic rate; Chol., cholesterol; T-ab, thyroglobulin antibodies; CFT, complement fixation test; TRC, tanned red cell; LE, lupus erythematosus preparation; γ-glob., gamma globulin; BP, blood pressure; ESR, erythrocyte sedimentation rate; RAI, radioactive iodine.

* 35 of these 38 patients had been described previously (Nilsson and Doniach, 1964).

of thyroid precipitin antibodies measured in our laboratory was extremely high; a similarly high level of thyroid antibodies was found by Stanford University School of Medicine Laboratory (Dr. K. B. Taylor), employing the immunofluorescent technique. Other studies performed in Dr. Taylor's laboratory revealed a weakly positive test for antibodies against human stomach parietal cells and are summarized in Table II.

A needle biopsy of the liver was reported to be normal. Histologically, an open biopsy of the thyroid showed extreme fibrosis with no recognizable thyroid follicles, and infiltration with a moderate number of plasma cells, but only a few lymphocytes (Fig. 1). Because of repeated complaints of epigastric pain, upper gastrointestinal serial x-ray films were taken on two occasions. There was no evidence of peptic ulcer disease.

Therapy with tri-iodothyronine was initiated and increased gradually to 100 μg. daily. Symptoms and signs of hypothyroidism gradually cleared, as did the pain in the ear and at the angle of the jaw. The thyroid gland became slightly smaller but continued to be very tender. Two months later therapy was changed to desiccated thyroid, 3 gr. daily. ESR 52, direct Coombs reaction strongly positive, and latex fixation test positive. Total serum protein was 7·9 g./100 ml.

Serum protein electrophoresis: albumin 4·1, α₁-globulin 0·1, α₂-globulin 0·7, β-globulin 0·8, and γ-globulin 2·2 g./100 ml.

Ten months later her gland was smaller and less tender. ESR 52; direct Coombs reaction positive, and latex fixation test positive. An LE preparation was negative and serum protein electrophoresis essentially unchanged, with a γ-globulin level of 3·0 g./100 ml. Despite the laboratory evidence of continued activity of her disease, she appeared generally to be in good health.

TABLE II
Auto-antibody Studies Performed on Patient's Serum

<i>Immunofluorescence</i>				
Human thyroid	..	..	..	++++
Human stomach parietal cell	..	..	..	Weak +
Calf thymus (antinuclear)	..	..	..	—
Anti-intrinsic factor (Ardeman-Chanarin test)	..	..	..	—
Rat kidney (mitochondria)	..	..	..	—
<i>Complement fixation</i>				
Anti-nuclear	..	..	..	<1:4
Gastric anti-cytoplasmic	..	..	..	<1:4

FIG. 1.—Low ($\times 27$) and high power ($\times 335$) photomicrographs of thyroid biopsy showing extensive lymphocytic infiltration and fibrosis.

Discussion

The first manifestations of lymphocytic thyroiditis in childhood may appear at any time in the first two decades. The youngest case reported was 3 months old at the onset. The age of onset (Fig. 2) shows a steady rise during the first decade, with a peak at the age of 11 to 12. Thereafter, there is a decline in incidence, and in only one case has the onset been reported between 17 and 19 years of age. There is an overwhelming preponderance of females, as only 7.3% of the cases in children have been male. The disease usually develops insidiously, and it may be many months or years before the condition is brought to the attention of a physician. In about one-third of the patients, enlargement of the thyroid gland was the first abnormality noted and this may be the only finding for many months. In a somewhat larger group of cases, other clinical manifestations develop simultaneously with or preceding the enlargement of the thyroid. The goitre is initially symmetrically and diffusely involved, and has a smooth finely granular or lobulated surface. The thyroid is characteristically non-tender; a thrill or bruit is occasionally present. The goitre is usually firm. Asymmetry and lobulation of the thyroid have occasionally been described. In some patients one or more nodules can be palpated when the patient is first seen, while in others the nodules first become evident after thyroid

treatment is initiated. Pressure symptoms may occur, and include a sense of heaviness or fullness in the neck and dysphagia. Hoarseness or change in the quality of the voice may occur. Slight compression of the trachea may be found on radio-

FIG. 2.—Age of onset in childhood in 132 cases of lymphocytic thyroiditis.

logical examination in children with local manifestations.

Signs of local inflammation of the thyroid gland are usually absent. Significant cervical lymphadenopathy is uncommon but occasionally reaches appreciable size and may be suggestive of thyroid carcinoma (Hahn, Hayles, and Woolner, 1965).

The majority of children fall within the normal range for height and weight, and general health is not impaired. When first diagnosed, the patients are generally euthyroid, but a few show evidence of mild to moderate hypothyroidism, or mild hyperthyroidism. Asymptomatic non-toxic goitre arising insidiously is probably the most common expression of chronic thyroiditis. However, as the patients are followed over a period of years, a significant proportion of them become hypothyroid. Saxena and Crawford (1962) found that nervousness, anxiety, emotional instability, and irritability formed important components of the clinical manifestations in many of their patients. Prominence of the eyes was occasionally present. The hypothyroid manifestations in many cases may be present and coincident with the first recognition of thyroid enlargement, or may not appear for several years. The incidence of lymphocytic thyroiditis in childhood is higher in the female, and the disease is more likely to become manifest at a time of endocrine transition, e.g. with the menarche.

Histologically, the thyroid gland shows diffuse interfollicular infiltration with plasma cells and lymphocytes, atrophy of the follicles, and varying degrees of epithelial degeneration. Focal collection of lymphocytes may be prominent; germinal follicles are usually present. Most commonly the follicles appear small, are lined by cuboidal non-oxophilic epithelium, and contain little or no colloid. Collections of macrophages within the otherwise empty follicles are commonly seen. In some cases the follicular epithelium shows a striking degree of hyperplasia of the columnar epithelium and some degree of papillary infolding with the lymphocytic infiltrates developing into localized prominent focal collections of lymphocytes and germinal centres with less marked interfollicular infiltration. In most cases fibrosis of the thyroid has not been a prominent feature in children. The marked and extensive fibrosis demonstrated in the open biopsy specimen from our patient is quite unusual. Atrophy is not uncommon.

One of the most characteristic laboratory abnormalities of lymphocytic thyroiditis is a difference of more than 1 $\mu\text{g}/100\text{ ml.}$ between the values of protein-bound iodine (PBI) and butanol-extractable iodine (BEI). Normally, the BEI is 0.5 to 1.0 $\mu\text{g.}$

less than the PBI, but Gribetz, Talbot, and Crawford (1954) showed that this difference between the PBI and BEI values was significantly increased in lymphocytic thyroiditis. PBI values vary considerably from levels well below the normal range to others which are significantly raised. In most children, the PBI is initially high or high-normal, with a tendency for the levels to drop subsequently. The increase in PBI probably results from the presence of abnormal iodoproteins which are hormonally inactive; such iodoproteins have been found in the serum and isolated from the thyroid glands of patients with various other thyroid diseases, including Graves' disease with exophthalmic goitre. The production of large amounts of abnormal iodoproteins may contribute to the genesis of non-toxic goitre by diverting iodine into metabolically inactive pools, with resultant chronically increased pituitary stimulation (TSH) which, in turn, produces increased enlargement of the gland.

Radioactive iodide (RAI) uptake is often increased but may be normal or low, perhaps reflecting the particular stage of the disease process. Although there is a rapid uptake of iodide by the gland, the iodide is not oxidized and incorporated normally into the tyrosyl-thyroglobulin complex. It is therefore easily released and this release may be enhanced by the administration of perchlorate or thiocyanate. The defect in hormonogenesis is presumably due either to a deficiency or to interference in the action of a peroxidase which converts iodide to iodine or to decreased activity of an iodotransferase enzyme which enhances the binding of iodine to tyrosine.

Some increase in serum γ -globulin levels occurs in childhood but is uncommon. Laboratory evidence of abnormalities of measurable immune mechanisms have frequently been described in lymphocytic thyroiditis. A rise of antibody titres to various thyroid gland fractions has been reported (Table III). However, the presence of antithyroid antibodies is not diagnostic of Hashimoto's thyroiditis. In common with other reported cases of lymphocytic thyroiditis with this degree of fibrosis and hypothyroidism, a high titre of antithyroid antibodies was present in our patient (Senhauser, Hazard, Williams, and Crile, 1962). Occasionally, a transient or prolonged 'false positive' reaction to rheumatoid factor (RF) or VDRL, or significant increase in the Coombs antibody titre may occur.

It has been suggested that the aetiology of thyroiditis involved the production of antibodies to thyroid protein, which were abnormally released following damage to the follicular basement membrane, and that these 'antithyroid antibodies' might

play a causal role in the destruction of the thyroid. However, the theory of thyroglobulin as a secluded antigen has had to be abandoned since Hjort and Pedersen (1962) showed that thyroglobulin circulates in normal adults and in cord blood (Beierwaltes, Dodson, and Wheeler, 1959; Blizzard, Chandler, Landing, Pettit, and West, 1960; Chandler, Blizzard, Hung, and Kyle, 1962). Moreover, it has not been possible to produce thyroiditis by transferring serum from 'immunized' into 'non-immunized' animals (Johnstone and Howland, 1961; Roitt and Doniach, 1958), indicating that the presence of circulating antibodies is not a significant factor in the production of auto-immune thyroiditis.

The unusual findings in our patient included the exquisite tenderness of the thyroid gland, the pressure symptoms, the presence of hypofunction of the thyroid, the increase in serum γ -globulins (up to 3.3 g./100 ml.) persisting for 16 months, the histopathological changes of the thyroid gland with extreme fibrosis and no recognizable thyroid follicles, and the presence of a positive Coombs reaction and

phoid infiltration without fibrosis. Saxena and Crawford (1962) in their series of 32 cases found 2 with pain in the area of the thyroid gland. There was nothing distinctive about the histological picture in these cases, and fibrosis was not a prominent finding. Nilsson and Doniach noted pain in only 3 of the 35 cases that they studied (Doniach, Nilsson, and Roitt, 1965; Nilsson and Doniach, 1964). One of these was an 11-year-old girl who had a subacute onset and became hypothyroid one year later; another was a 16-year-old girl who had been myxoedematous for approximately four years; the γ -globulin level was raised in both patients. Doniach, Hudson, and Roitt (1960) reported an 18-year-old girl who had painful swelling of the thyroid; she also had paraesthesiae of the legs and arms and a hypochondriacal neurosis or early schizophrenia. In this patient the γ -globulin level was normal. Schilling (1945) described a 15-year-old girl with Hashimoto's thyroiditis who presented with rapid thyroid enlargement of three months' duration and occasional sharp pains radiating to the right side of the neck and ear.

As previously noted, significant increases in serum γ -globulin levels are quite unusual in children with lymphocytic thyroiditis. In adults a slight to moderate increase in γ -globulin concentration was noted in 50% of the cases. The maximum level reported at any age was 2.9 g./100 ml. (Shulman, Rose, and Witebsky, 1960). The level of 3.3 g./100 ml. in our patient represents the highest value reported in this disease.

Riedel's struma was not a consideration in this case as the thyroid gland was not 'stony hard', and the open biopsy failed to demonstrate invasive fibrosis extending beyond the thyroid capsule to extrathyroidal tissue structures.

Summary

An unusual case of lymphocytic (auto-immune, Hashimoto's) thyroiditis in a 14-year-old girl is described. The findings of note included: exquisite tenderness of the thyroid gland associated with pressure symptoms, severe hypothyroidism, histological appearance of extensive fibrosis, and persistent hyper- γ -globulinaemia, with pronounced increases in antithyroid antibodies.

A brief summary of the world literature of lymphocytic thyroiditis in childhood is presented.

REFERENCES

- Becker, K. L., Titus, J. L., Woolner, L. B., and McConehey, W. M. (1965). Significance of morphologic thyroiditis. *Ann. intern. Med.*, **62**, 1134.

TABLE III

Demonstrable Antithyroid Antibodies Reported to Date

Antigen	Test for Antibody Detection
Thyroglobulin (CA ₁)	(1) Precipitin (2) Tanned red cell haemagglutination (3) Latex particle agglutination (4) Coons fluorescent staining, using fixed thyroid sections
Microsomal component	(1) Complement fixation (2) Coons fluorescent staining, using unfixed thyroid sections (3) Detection of cytotoxic factor, using thyroid tissue culture
Second colloid (CA ₂)	(1) Coons fluorescent staining, using fixed thyroid sections, after absorption of the serum with thyroglobulin

latex flocculation test in association with a high titre of antithyroid antibodies. Although several of these findings are more consistent with adult cases of Hashimoto's disease, the exquisite tenderness, high serum γ -globulin level, and extensive fibrosis are rare at any age (Farber and Vawter, 1961; Nilsson and Doniach, 1964; Saxena and Crawford, 1962). Indeed, our review of the published reports failed to reveal a single case with a degree of pain and tenderness similar to that of our patient. Farber and Vawter (1961) described a 15-year-old girl with mild discomfort in the anterior neck radiating to the ear, and slight tenderness of the gland. Histologically, there was considerable lym-

- Beierwaltes, W. H., Dodson, V. N., and Wheeler, A. H. (1959). Thyroid autoantibodies in the families of cretins. *J. clin. Endocr.*, **19**, 179.
- Berglund, G., Broberger, O., and Zetterström, R. (1960). Hashimoto's disease in childhood: clinical and immunological study of 5 cases. *Acta paediat. (Uppsala)*, **49**, 663.
- Blizzard, R. M., Chandler, R. W., Landing, B. H., Pettit, M. D., and West, C. D. (1960). Maternal autoimmunization to thyroid as a probable cause of athyrotic cretinism. *New Engl. J. Med.*, **263**, 327.
- Bogart, L. M. (1938). In discussion to Lehman, J. A., Hashimoto's struma. *Trans. 3rd int. Goiter Conf. and Amer. Ass. for Study of Goiter, Washington, D.C.*, 244.
- Brecher, I. N., Hirsch, E., and Gould, E. A. (1965). Thyroiditis and surgery: a review of 81 cases. *Amer. Surgn.*, **31**, 53.
- Brown, H., and McGarity, W. C. (1959). Chronic thyroiditis in childhood. *J. Amer. med. Ass.*, **171**, 1182.
- Buffat, J. D. (1963). La thyroïdite d'Hashimoto. *Helv. chir. Acta*, **30**, 6.
- Buxton, R. W. (1957). Thyroid disease in childhood. *Sth. med. J. (Bgham, Ala.)*, **50**, 1175.
- Chandler, R. W., Blizzard, R. M., Hung, W., and Kyle, M. (1962). Incidence of thyrocytotoxic factor and other antithyroid antibodies in the mothers of cretins. *New Engl. J. Med.*, **267**, 376.
- Chimenes, H., Klotz, H. P., and Sors, C. (1961). Histoire naturelle de la maladie de Hashimoto. *Sem. Hôp. Paris*, **37**, 3175.
- Clayton, G. W., and Johnson, C. M. (1960). Struma lymphomatosa in children. *J. Pediat.*, **57**, 410.
- Davis, H. C., and Hanske, E. A. (1955). Hashimoto's disease in childhood. *Amer. J. Dis. Child.*, **90**, 173.
- Davison, T. C., and Letton, A. H. (1949). Hashimoto's disease. *J. clin. Endocr.*, **9**, 980.
- De Groot, L. J., Hall, R., McDermott, W. V., Jr., and Davis, A. M. (1962). Hashimoto's thyroiditis: a genetically conditioned disease. *New Engl. J. Med.*, **267**, 267.
- Doniach, D., Hudson, R. V., and Roitt, I. M. (1960). Human auto-immune thyroiditis: clinical studies. *Brit. med. J.*, **1**, 365.
- , Nilsson, L. R., and Roitt, I. M. (1965). Autoimmune thyroiditis in children and adolescents. II. Immunological correlations and parent study. *Acta paediat. (Uppsala)*, **54**, 260.
- Dunning, E. J. (1959). Struma lymphomatosa: a report of 3 cases in one family. *J. clin. Endocr.*, **19**, 1121.
- Farber, S., and Craig, J. M. (1958). Clinical pathological conference. The Children's Hospital Medical Center, Boston, Mass. *J. Pediat.*, **53**, 494.
- , and Vawter, G. F. (1961). Clinical pathological conference. The Children's Hospital Medical Center, Boston, Mass. *ibid.*, **59**, 777.
- Frid, G., and Wijnblad, H. (1957). Subacute thyroiditis struma lymphomatosa (Hashimoto's disease), and chronic fibrous invasion goitre (Riedel's disease). *Acta chir. scand.*, **112**, 170.
- Gribetz, D., Talbot, N. B., and Crawford, J. D. (1954). Goiter due to lymphocytic thyroiditis (Hashimoto's struma); its occurrence in preadolescent and adolescent girls. *New Engl. J. Med.*, **250**, 555.
- Hahn, H. B., Jr., Hayles, A. B., and Woolner, L. B. (1965). Lymphocytic thyroiditis in children. *J. Pediat.*, **66**, 73.
- Hashimoto, H. (1912). Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa). *Arch. Klin. Chir.*, **97**, 219.
- Hellwig, C. A. (1938). Lymphadenoid goiter. *Arch. Path.*, **25**, 838.
- Hendrick, J. W. (1957). Diagnosis and management of thyroiditis. *J. Amer. med. Ass.*, **164**, 127.
- Hjort, A., and Pedersen, G. T. (1962). Thyroid antibodies and 'thyroglobulin' in the serum in pregnant and parturient women and in newborn infants. *Lancet*, **2**, 259.
- Houston, W., and Shee, J. C. (1963). Auto-immune thyroiditis: its diagnosis and treatment. *Practitioner*, **191**, 55.
- Hung, W., and Winship, G. T. (1963). Struma lymphomatosa in mother and daughter with serologic and histologic evidence. *J. clin. Endocr.*, **23**, 465.
- Johnstone, D. E., and Howland, J. (1961). Autoimmune thyroiditis induced by gamma irradiation and by passive transfer of antithyroid antibodies. *Amer. J. Dis. Child.*, **102**, 505.
- Joll, C. A. (1939). The pathology, diagnosis, and treatment of Hashimoto's disease (struma lymphomatosa). *Brit. J. Surg.*, **27**, 351.
- Jubin, E. J., Schmid, J. R., and Berchtold, R. (1964). Die aseptische Thyroiditis Hashimoto und de Quervain. *Schweiz. med. Wschr.*, **94**, 484.
- Klein, E. (1965). Strumen im Wachstumsalter. *Internist (Berl.)*, **6**, 30.
- Lasser, R. P., and Grayzel, D. M. (1949). Subacute thyroiditis, struma fibrosa, struma lymphomatosa: a clinical-pathological study. *Amer. J. med. Sci.*, **217**, 518.
- Leboeuf, G., and Bongiovanni, A. M. (1964). Thyroiditis in childhood. *Advanc. Pediat.*, **13**, 183.
- Lindsay, S., Dailey, M. E., Friedlander, J., Yee, G., and Soley, M. H. (1952). Chronic thyroiditis: a clinical and pathological study of 354 patients. *J. clin. Endocr.*, **12**, 1578.
- Lyday, R. O. (1957). Struma lymphomatosa (Hashimoto's disease) in children. *Amer. J. Surg.*, **94**, 417.
- McGuillan, A. S. (1938). Thyroiditis. *Trans. 3rd inter. Goiter Conf. and Amer. Ass. for Study of Goiter, Washington, D.C.*, 212.
- Macksood, W., Rapport, R. L., and Hodges, F. (1961). The increasing incidence of Hashimoto's disease. *Arch. Surg.*, **83**, 384.
- Marshall, S. F., and Meissner, W. A. (1955). Struma lymphomatosa (Hashimoto's disease). *Ann. Surg.*, **141**, 737.
- Nilsson, L. R., and Doniach, D. (1964). Auto-immune thyroiditis in children and adolescents. I. Clinical studies. *Acta paediat. (Uppsala)*, **53**, 255.
- Norris, W. J., and Pollock, W. F. (1955). Nodular goiters in children. *Amer. J. Surg.*, **90**, 345.
- Owen, C. A., Jr., and McConahey, W. M. (1956). An unusual iodinated protein of the serum in Hashimoto's thyroiditis. *J. clin. Endocr.*, **16**, 1570.
- Paris, J., McConahey, W. M., Tauxe, W. N., Woolner, L. B., and Bahn, R. C. (1961). The effects of iodides on Hashimoto's thyroiditis. *ibid.*, **21**, 1037.
- Parmley, C. C., and Hellwig, C. A. (1946). Lymphadenoid goiter. *Arch. Surg.*, **53**, 190.
- Ricca, J. J., Morrione, T. G., and Adel, H. (1956). Struma lymphomatosa (Hashimoto's disease). *Amer. J. Dis. Child.*, **92**, 592.
- Roitt, I. M., and Doniach, D. (1958). Human auto-immune thyroiditis: serological studies. *Lancet*, **2**, 1027.
- Saxena, K. M., and Crawford, J. D. (1962). Juvenile lymphocytic thyroiditis. *Pediatrics*, **30**, 917.
- Schilling, J. A. (1945). Struma lymphomatosa, struma fibrosa and thyroiditis. *Surg. Gynec. Obstet.*, **81**, 533.
- Schlicke, C. P., Hill, J. E., and Schultz, G. F. (1960). Carcinoma in chronic thyroiditis. *ibid.*, **111**, 552.
- Senhauser, D. A., Hazard, J. B., Williams, F. C., and Crile, G., Jr. (1962). The incidence of circulating thyroid antibodies, as measured by means of two agglutination technics. *Amer. J. clin. Path.*, **38**, 482.
- Shands, W. C. (1960). Carcinoma of the thyroid in association with struma lymphomatosa (Hashimoto's disease). *Ann. Surg.*, **151**, 675.
- Shulman, S., Rose, N. R., and Witebsky, E. (1960). The antibody molecule in chronic nonspecific thyroiditis: electrophoretic patterns of serum. *J. Lab. clin. Med.*, **55**, 733.
- Skillern, P. G., Crile, G., Jr., McCullaugh, E. P., Hazard, J. B., Lewis, L. A., and Brown, H. (1956). Struma lymphomatosa: primary thyroid failure with compensatory thyroid enlargement. *J. clin. Endocr.*, **16**, 35.
- Statland, H., Wasserman, M. M., and Vickery, A. L. (1951). Struma lymphomatosa (Hashimoto's struma). *Arch. intern. Med.*, **88**, 659.
- Wilkins, L. (1957). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 2nd ed. C. C. Thomas, Springfield, Illinois.
- Wolfson, S. L., and Kahana, L. (1965). Hashimoto's thyroiditis. Report of case in a child. *J. Fla. med. Ass.*, **52**, 316.
- Woolner, L. B., McConahey, W. M., and Beahrs, O. H. (1959). Struma lymphomatosa (Hashimoto's thyroiditis) and related thyroidal disorders. *J. clin. Endocr.*, **19**, 53.
- Van Wyk, J. J., Wynn, J. O., Deiss, W. P., Arnold, M. B., and Graham, J. B. (1962). Genetic studies in a family with "simple" goiter. *ibid.*, **22**, 399.
- Zaino, E. C., and Guerra, W. (1964). Hashimoto's disease (struma lymphomatosa) in identical twins. *Arch. intern. Med.*, **113**, 70.