Etiology, Pathogenesis and Management of Thyroiditis

Dr Sunil Malla Bujar Barua
Moderator: Dr Anjali Mishra
INTRODUCTION

- Thyroiditis is defined as an inflammatory disorder of the thyroid gland.
- It may result from a myriad of etiologies and is usually classified into acute, subacute, and chronic forms.
- Each of these is associated with a distinct clinical presentation and histology.

Textbook of Endocrine Surgery
edited by Orlo H. Clark, Quan-Yang Duh, Electron Kebebew. - 2nd ed.
Classification

From commonest to least common

• Hashimoto’s thyroiditis
• Subacute lymphocytic thyroiditis
  – Postpartum
  – Sporadic silent
• Subacute granulomatous thyroiditis (De Quervain’s thyroiditis)
• Drug-induced thyroiditis
• Radiation thyroiditis
• Acute suppurative/infectious thyroiditis
  – Bacterial, Fungal, Parasitic
• Invasive fibrous thyroiditis (Riedel’s thyroiditis)
• Miscellaneous
  – Sarcoid, Amyloid, Traumatic, Palpation-induced
Classification

- Acute
- Subacute
- Chronic

- Painless
- Painful
Acute (Suppurative) Thyroiditis

- Acute thyroiditis was first described by Bauchet in 1857 and accounted for approximately 0.1% of thyroid surgeries before the advent of antibiotic therapy
Etiology and Pathogenesis

- The thyroid gland has an innate resistance to infection due to
  - extensive blood and lymphatic supply
  - high iodide content
  - fibrous capsule
- Immunosuppression –
  - acute suppurative thyroid infections and necrosis have been described in patients with
    - AIDS
    - those undergoing aggressive chemotherapy for hematologic malignancies.
- Acute thyroiditis may be caused by infectious agents that seed the thyroid gland
  - (1) by the hematogenous or lymphatic route
  - (2) by direct spread from persistent pyriform sinus fistulas or thyroglossal duct cysts, or
  - (3) as a result of penetrating trauma to the thyroid gland
Jian Zhang, Shaohong Huang, Hui Li, Yun Li, Huiguo Chen, Lijia Gu. Relapsing suppurative neck abscess after chemocauterization of pyriform sinus fistula. Clinical Imaging - 13 February 2012 (10.1016/j.clinimag.2012.01.023)
Takai and associates demonstrated that acute suppurative thyroiditis can result from persistent pyriform sinus fistulas.

- Responsible for a large proportion of cases of recurrent acute thyroiditis.
- Fistulas - believed to be fourth branchial pouch remnants
  - originate at the apex of the pyriform fossa.
  - tract courses in an antero-inferior direction to end blindly in the perithyroidal space or the thyroid parenchyma.
  - infection may lead to acute thyroiditis or soft tissue abscesses, which can secondarily extend to the thyroid.

Bacterial Profile

• Commonest (Oral cavity bacteria) : 70%
  – Staphylococcus
  – Streptococcus species
  – Anaerobes

• Less common
  – Escherichia coli
  – Pseudomonas aeruginosa
  – Haemophilus influenzae
  – Eikenella corrodens
  – Corynebacterium species

• Rare
  – Mycobacteria
  – Salmonella
  – Aspergillus
  – Actinomycoses species

• Pneumocystis carinii : in patients with AIDS

Histologic Features

- Usually arises in a normal thyroid gland
- Occurrence in a multinodular gland is not uncommon
- Histologically
  - intense inflammatory response
  - numerous polymorphonuclear leukocytes, lymphocytes
  - necrosis of the thyroid gland and abscess formation often ensue
16/10/2012
Thyroiditis
Clinical Presentation

• Children and young adults
• Occurs equally in both sexes
• Often preceded by an upper respiratory tract infection or otitis media
  – Severe neck pain radiating to the jaws or ear
  – fever
  – chills
  – odynophagia
  – dysphonia
• Infants
  – may present with respiratory distress and stridor secondary to tracheal compression caused by a thyroid abscess.
• Rarely may cause transient vocal cord palsy
• Erythematous skin usually overlies an extremely tender thyroid gland
• Patient holds the neck in a flexed position to avoid stretching the overlying strap muscles
• Fluctuance indicates an underlying abscess
• More frequent on the left side
  – reflects the left-sided predominance of pyriform sinus fistulas
  – thought to be due to
    • embryologic asymmetry of the transformation of the fourth branchial arch to form the aortic and innominate arteries or
    • to poor development of the ultimobranchial body on the right side of the embryo
Complications

• Systemic sepsis
• Tracheal or esophageal rupture
• Jugular vein thrombosis
• Laryngeal chondritis and perichondritis
• Sympathetic trunk paralysis
Differential Diagnosis

- Subacute painful thyroiditis
- Hashimoto's thyroiditis
- Suppurative lymphadenitis
- Thyroid carcinoma
- Thyroglossal duct or branchial cleft cyst
- Ludwig's angina
- Dissecting retropharyngeal abscess
- Laryngeal and esophageal carcinomas have also been reported to present as acute thyroiditis
• Distinguished by clinical history, physical examination, and diagnostic tests

• Lin and colleagues concluded that patients with malignancy were
  – older
  – more likely to have a history of dysphonia,
  – right thyroid lobe involvement,
  – larger lesions,
  – anemia, and
  – sterile thyroid aspirates.

Diagnostic Tests

• Blood tests reveal leukocytosis and an elevated erythrocyte sedimentation rate (ESR).
• Blood cultures are useful to identify the causative organisms.
• Thyroid function tests –
  – usually normal, although
  – transient elevations of triiodothyronine (T3) and thyroxine (T4) may occur as a result of release of pre-formed hormone from the inflamed gland.
• Radioactive iodine uptake (RAIU) scans –
  – usually normal or
  – decreased uptake due to suppression of thyroid-stimulating hormone (TSH) by the release of thyroid hormones.
  – If a thyroid abscess is present, an area of decreased uptake will be seen on the scan.
• Ultrasound is helpful to distinguish solid from cystic lesions
• Fine-needle aspiration (FNA) biopsy for Gram stain, culture, and cytology confirms the diagnosis and helps guide antibiotic therapy and diagnose underlying malignancy
• Barium swallow –
  – demonstrates pyriform sinus fistula tract with 80% sensitivity
  – False-negative results are usually due to edema around the tract orifice during acute infection
  – should be performed after antibiotic therapy during the quiescent phase
• Direct laryngoscopy is also helpful in identifying the tract
TREATMENT

• Patients should be treated with parenteral antibiotics based on the results of the Gram stain and culture.
• Abscesses are treated by drainage, either by aspiration with a wide-bore needle or open surgical drainage
• In patients with pyriform sinus fistulas, complete resection of the sinus tract, including the area of the thyroid where the tract ends, is recommended.
• Miyauchi and coworkers have demonstrated that complete fistulectomy is essential for cure
• Methylene blue infiltration via a Fogarty catheter is sometimes used to cannulate the tract and facilitate its identification and dissection

Subacute Thyroiditis
Painful (de Quervain's) Thyroiditis

- First described by Fritz de Quervain in 1904
- Most common cause of a painful thyroid gland.
- Other eponyms for this condition include
  - granulomatous thyroiditis
  - subacute granulomatous thyroiditis
  - pseudogranulomatous thyroiditis
Etiology and Pathogenesis

• Thought to be viral in origin or result from a post-viral inflammatory response. This theory is supported by the following observations:
  1. Frequently preceded by a respiratory infection, is usually self-limiting, and has a seasonal distribution (summer and fall).
  2. It is often associated with specific viral infection outbreaks such as
     – coxsackievirus
     – mumps
     – measles
     – adenovirus, and
     – infectious mononucleosis
  3. Cytopathic viruses have been cultured from thyroid tissue
  4. Viral antibodies have been detected in the sera of patients with the disease

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Thyroiditis
• Evidence for genetic predisposition - strong association with the **HLA-B35** haplotype
• A model of pathogenesis suggests that antigens (viruses or damaged thyroid tissue) → presented by macrophages (HLA-B35) → stimulate cytotoxic T lymphocytes
• Lymphocytes → damage thyroid follicular cells
• Autoimmune process is self-limiting.
• Antibodies directed against the TSH receptor have also been described
  – seem to be related to the inflammatory process
  – not believed to cause the disease
Histology

- Inflammatory process may involve the entire gland or a single lobe.
- Cut section-involved areas are firm and yellow-white.
- Microscopically-changes vary with the stage of the disease, may overlap.
- Microabscesses, -
  - result from neutrophil replacement of disrupted follicles,
  - Common in early inflammatory stage
- Later, lymphocytes, histiocytes, and plasma cells accumulate around damaged follicles.
- Colloid- surrounded by multinucleated giant cells, giving this disorder the designation of granulomatous thyroiditis.
Clinical Presentation

• Occurs more commonly in women (male-female ratio of 1:3 to 1:6) between 30 and 40 years of age.
• Sudden or gradual onset of unilateral or bilateral pain in the neck, which may radiate toward the mandible or ear and is exacerbated by swallowing or neck movement.
• Many cases-preceding upper respiratory tract infection with low-grade fever, neck pain, dysphagia, and flu-like symptoms with malaise and myalgias.
• Physical examination reveals an enlarged, exquisitely tender thyroid gland that is firm, particularly in the acute phase.
• The overlying skin may be erythematous if the inflammation is severe.
• Rarely, patients may present with high fever, toxicity, and pronounced edema leading to obstructive symptoms.
Clinical Presentation..

• The disorder classically progresses through four stages
  • **Hyperthyroid phase,**
    – due to release of thyroid hormone
    – lasts 3 to 6 weeks
    – tremors, sweating, palpitations, and heat intolerance in 50% to 70% of patients
  • Patients then progress to the second or **euthyroid** phase
  • **Hypothyroidism**
    – occurs in about 20% to 30% of patients
    – lasts from weeks to months
  • The last phase is characterized by resolution of the disease
    – returns to the **euthyroid** state in more than 90% of patients.
  • Some patients may progress directly from the hyper-thyroid phase to the recovery phase
  • A few patients develop recurrent disease
DIFFERENTIAL DIAGNOSIS

• Disorders that mimic the presentation of subacute thyroiditis include
  – hemorrhage into a thyroid nodule or cyst
  – acute suppurative thyroiditis
  – painful Hashimoto's thyroiditis
  – infected thyroglossal duct or branchial cleft cyst
  – pseudothyroiditis

• Pseudothyroiditis is produced by rapid growth of anaplastic or poorly differentiated thyroid malignancies
Diagnosis

- In the **early stages** of the disease, TSH is decreased, and thyroglobulin, T4, and T3 levels are elevated due to the release of preformed thyroid hormone and colloid from destroyed follicles.
- In contrast with Graves' disease, T4 and T3 are elevated in proportions reflecting their intrathyroidal content.
- Thyroid antibody titers (antithyroglobulin, antimicrosomal, and TSH receptor antibody) are also elevated in 10% to 20% of patients, → bear no relationship to the state of thyroid function.
- Most characteristic abnormality is an elevation of the ESR greater than 100 mm/hr. In fact, a normal ESR rules out active subacute thyroiditis.
Diagnosis..

- **RAIU** decreased (<2% at 24 hours) even in euthyroid patients
  - destruction of the thyroid parenchyma and iodine-trapping mechanism
  - release of thyroid hormones with TSH suppression
  - RAIU returns to normal as the process resolves
- **FNA biopsy** may be useful in
  - equivocal cases
  - to rule out malignancy
  - acute thyroiditis
- **Thyroid ultrasound** shows
  - areas of hypo-echogenicity that disappear as the disease process resolves
  - usefulness in predicting autoimmune thyroid disease in a multicenter study
Treatment

- **Self-limited**
- Usually resolves within a few months without specific therapy.
- Treatment primarily symptomatic
- **Aspirin** and other nonsteroidal anti-inflammatory drugs are often the initial medications of choice for pain relief
- **Prednisone** (40 mg/day-for early relief of pain and swelling in more severe cases.
- These drugs do not alter the underlying disease process
- Dose is usually tapered after a week and then discontinued within 2 to 4 weeks
- If pain and swelling recur during the taper or after withdrawal, the treatment is restarted
- Hyperthyroidism may rarely require treatment with **beta-blockers**
Treatment

- **Thyroid replacement** may be needed in the hypothyroid phase, if patients are symptomatic.
- Therapy should be withdrawn and the patient re-evaluated after 6 months.
- External-beam radiation therapy has been abandoned:
  - slower and less predictable response than steroids
  - approximately 25% failure rate
  - risk of thyroid cancer formation
- **Thyroidectomy** is reserved for the rare patient who has a prolonged course not responsive to medical measures.
Sequelae

- Recurrence
- Permanent Hypothyroidism
Silent (painless) Thyroiditis

- Usually comes to clinical attention because of symptoms of thyrotoxicosis caused by leakage of thyroid hormone from a painless thyroid gland.
- Often occurs in the post-partum period


- Also known as
  - lymphocytic thyroiditis with spontaneously resolving hyperthyroidism
  - subacute lymphocytic thyroiditis,
  - painless lymphocytic thyroiditis,
  - painless thyroiditis, or
  - silent thyroiditis.

- Painless thyroiditis may occur sporadically or in the postpartum period.

Incidence

- Varies geographically
- Patients usually between 30-60 years
- Female: male = 1.5:1
- Rarely diagnosed unless associated with pregnancy
- 5-9% of women in the 1st year after delivery especially in patients with circulating antibody against thyroid peroxidase
Etiology

- Autoimmune
- Family history of thyroid disease
- Post-partum associated with HLA-D3 and HLA-D5
- Exposure to
  - iodine e.g. amiodarone
  - Lithium
  - Interleukin-2
  - Interferon
- Associated with other autoimmune diseases
  - Rheumatoid arthritis
  - Systemic sclerosis
  - Grave’s disease
  - Primary adrenal insufficiency
  - Systemic lupus erythematosus

Pathology

• The thyroid gland may be asymmetrically enlarged on gross inspection
• Microscopic examination reveals a multifocal inflammatory infiltrate, consisting chiefly of small lymphocytes
• Scattered areas of disrupted and collapsed thyroid follicles are also present
• Unlike Hashimoto's thyroiditis, plasma cells and germinal centers are not conspicuous, and this feature is helpful in distinguishing the two conditions.
Clinical Presentation

• The clinical course parallels painful thyroiditis and is characterized by four stages-
  1. thyrotoxic (occurs 1 to 3 months' postpartum)
  2. euthyroid
  3. hypothyroid (occurs at 3 to 6 months' postpartum)
  4. euthyroid again (occurs by 1 year)
• Only about 30% of all patients follow this classic sequence of events
• Thyrotoxicosis or hypothyroidism alone is the presenting features in about 35% and 40% of patients, respectively.
• When hyperthyroid symptoms occur, they are transient and characterized by tachycardia, palpitations, heat intolerance, nervousness, and weight loss.
• Hypothyroid phase is more pronounced in terms of symptoms.
• Normal-sized or slightly enlarged, slightly firm, non-tender gland.
**Figure 6.** Postpartum thyroiditis. Note the diffuse thyroid gland hypoechogenicity permeated by even more hypoechogenic areas.
Treatment

• Specific treatment - sometimes required in patients with severe symptoms.
• Beta blockers → control symptoms of hyperthyroidism
• Antithyroid drugs - not necessary: no increase in thyroid hormone synthesis
• Corticosteroids
  – sometimes used to shorten the hyperthyroidism phase
  – generally not helpful
• Thyroid hormone replacement → patients with hypothyroidism
• Thyroidectomy is indicated only for the rare patients with recurrent, disabling episodes of thyroiditis
• RAI ablation of the thyroid may also be used in these rare cases.
Sequelae

• Recurrence
• Hypothyroidism
Atypical Subacute Thyroiditis

- Variants of subacute thyroiditis, designated atypical sub-acute thyroiditis, have also been described.

- Patients may present with features of painful thyroiditis but lack the HLA-B35 haplotype or present with painless thyroiditis without evidence of thyroid autoimmunity.

- Further studies are needed to characterize this variant adequately.
Chronic Thyroiditis

Lymphocytic (Hashimoto's) Thyroiditis

- First described by Hashimoto Haraku in 1912 as struma lymphomatosa-a transformation of thyroid tissue to lymphoid tissue
- Roittand colleagues demonstrated thyroid autoantibodies in patients with this disease
- Chronic autoimmune thyroiditis - two different clinical manifestations:
  - atrophic
  - goitrous
- Goitrous is also known as Hashimoto's thyroiditis → most common inflammatory disease of the thyroid
- Prevalence rates of chronic autoimmune thyroiditis vary depending on the criteria used for diagnosis
• Autopsy studies demonstrate that 40% to 45% of women and 20% of men in the United States and United Kingdom have focal thyroiditis
• Most autopsy and thyroid antibody studies document Hashimoto's thyroiditis in approximately 17% of women in the United States and Japan
• A recent review of population-based studies with strict criteria for the diagnosis of Hashimoto's thyroiditis reported a prevalence of 0.79% in adults with an incidence of 22 per 100,000 inhabitants.


Etiology and Pathogenesis

- **T Cells, Autoantibodies, and Apoptosis**
- Thought to be initiated by the activation of CD4+ T (helper) lymphocytes with specificity for thyroid antigens.
- Mechanism of activation of these cells is not completely understood.
- One hypothesis centers on molecular mimicry
  - postulates that viral or bacterial infection with proteins similar to thyroid proteins leads to the activation of thyroid-specific lymphocytes.
- Serologic evidence of such infection has been documented in patients with chronic autoimmune thyroiditis
  - cumulative evidence is not convincing
- More widely accepted hypothesis suggests that thyroid cells themselves present intracellular proteins to helper T cells.
Thyroid cells do not normally express HLA class II molecules

IFN-γ receptor

thymus epithelial cell

IFN-γ produced during infection or nonspecific inflammation induces HLA class II expression on thyroid cells

IFN-γ

HLA class II molecules

thymus epithelial cell

Activated T cells recognize thyroid peptides presented by HLA class II and induce autoimmune thyroid disease

CD4 TCR IFN-γ

Autoimmune thyroid disease

Figure 11-32 The Immune System, 2/e (© Garland Science 2005)
Theory support-

Unlike normal thyrocytes, thyroid cells of patients with autoimmune thyroiditis express the major histocompatibility complex (MHC) class II proteins (HLA-DR, HLA-DP, and HLA-DQ) which are required for antigen presentation to CD4+ helper cells.

Activated T cells release the cytokine interferon gamma, which further promotes the expression of these MHC molecules and thus perpetuates the autoimmune process.

Once activated, T cells can recruit cytotoxic CD8+ T cells to the thyroid.

Hypothyroidism is believed to result mainly from the destruction of thyrocytes by these cells.

T-helper cells also recruit self-reactive B cells to the thyroid and stimulate them to secrete autoantibodies. These antibodies are directed against three main antigens:

- thyroglobulin,
- TPO (microsomal antigen)
- thyrotropin receptor

Antibodies to the sodium-iodine symporter (NIS) have also been reported in patients with Hashimoto's thyroiditis although more recent studies indicate that they are not as important as previously thought.
• Autoantibodies can also cause hypothyroidism via blockage of their ligands, fixation of complement, and antibody-mediated cytotoxicity (natural killer cells).
• However, the relative contributions of these mechanisms to thyrocyte destruction in vivo remain unresolved.
• Apoptosis (programmed cell death) has also been implicated in the pathogenesis of Hashimoto's thyroiditis.
• Thyrocytes from patients with this disease consistently show increased expression of death receptors such as FasL and decreased levels of the anti-apoptotic molecule Bcl2 when compared to cells from patients with Graves'disease.
• **Environmental Factors**

• The prevalence of chronic autoimmune thyroiditis parallels that of iodine intake

• Supplementation in iodine-deficient areas increases thyroid lymphocytic infiltration and prevalence of thyroid antibodies

• Supplementation in iodine-replete regions leads to reversible hypothyroidism by inhibition of the biosynthesis and release of thyroid hormone.

• Various drugs have also been implicated in the etiology of chronic thyroiditis

• The effects of these medications are more pronounced in patients with thyroid antibodies than in those without antibodies.
• Treatment with interferon alpha, interleukin 2 or granulocyte-macrophage colony-stimulating factor $\rightarrow$ reversible formation of thyroid autoantibodies, hypothyroidism, or Graves'disease.
• Iodine-rich diet $\rightarrow$ thyroiditis in chickens and beagle dogs
• Genetic predisposition. Evidence $\rightarrow$ from both experimental and spontaneously occurring animal models of autoimmune thyroiditis and human studies
• Human family studies $\rightarrow$ increased incidence of thyroid autoantibodies (up to 46%) in first-degree relatives of patients with Hashimoto's thyroiditis
• Segregation analyses indicate that this susceptibility is inherited in a mendelian dominant fashion with high penetrance.
• However, Hashimoto's thyroiditis does not exhibit classic mendelian inheritance, and genetic predisposition appears to be complex, possibly caused by many disease-associated alleles located at different genetic loci
• Occurrence of autoantibodies and hypothyroidism in patients with specific chromosomal abnormalities such as Turner's and Down syndromes
• Part of the genetic susceptibility to Hashimoto's thyroiditis may reside on the chromosomes X and 21
• Associations with HLA-B8, -DR3, and –DR5 haplotypes of the major histocompatibility complex have also been described
• HLA locus is not believed to be a major etiologic factor
Figure 2. Doppler mapping showing a diffuse hypervascularization pattern.
Histology

- The thyroid gland is generally mildly enlarged throughout and has a pale, grayish tan cut surface that is firm and slightly nodular.
- On microscopic examination, the gland is diffusely infiltrated by mononuclear cells (small lymphocytes and plasma cells) and occasionally shows well-developed germinal centers.
- Thyroid follicles are smaller than normal with reduced amounts of colloid.
- The follicles are lined by Hurthle or Askanazy cells, which are characterized by abundant eosinophilic, granular cytoplasm.

http://www.pathologystudent.com/?p=354
Histology..

- The amount of interstitial connective tissue is increased and manifests itself as fibrosis.
- In contrast to Riedel's thyroiditis, the fibrosis does not extend beyond the gland itself.
- In atrophic chronic thyroiditis, the fibrosis is more pronounced.
- Existing evidence does not support the progression of the goitrous form to the atrophic form.
Clinical Presentation

• Like other autoimmune diseases, Hashimoto's thyroiditis is also more common in women (male-female ratio, 1:10 to 20) between the ages of 30 and 50 years.
• The most common presentation is that of a relatively small, firm, and granular gland discovered on routine physical examination or the awareness of a painless anterior neck mass.
• In unusual cases, the thyroid gland may enlarge rapidly, causing compressive symptoms and dysphonia.
• Pain, especially radiating to the ear, is a rare manifestation.
Clinical Presentation..

- Approximately 20% of patients present with hypothyroidism whereas 5% present with hyperthyroidism (hashitoxicosis).
- In classic goitrous Hashimoto's thyroiditis, physical examination reveals a diffusely enlarged, firm gland that is also lobulated.
- An enlarged pyramidal lobe is usually palpable.
- The goiter may be asymmetrical, and, rarely, nodules and enlarged lymph nodes may be palpated.
- Thyroid-associated ophthalmopathy occurs rarely in patients with chronic autoimmune thyroiditis.
Diagnosis

• When Hashimoto's thyroiditis is suspected clinically, an elevated TSH level and thyroid autoantibodies confirm the diagnosis.
• About 95% of patients have increased antimicrosomal antibody titers, whereas anti thyroglobulin antibodies are positive in about 60% of patients.
• The microsomal antigen has been identified as TPO (the rate-limiting enzyme in thyroid biosynthesis).
• Anti-TPO antibodies measured by radioimmunoassay are a more sensitive indicator of Hashimoto's thyroiditis than are antimicrosomal antibodies detected by hemagglutination studies.
• Antibodies to the TSH receptor are present in up to 60%, and antibodies to NIS can be found in 25% of patients.
• RAIU is variable and may mimic Graves' disease, multi-nodular goiter, or a hot or cold nodule.
• However, the RAIU is usually normal or elevated, even in hypothyroid patients, and thus allows differentiation from subacute thyroiditis.
Diagnosis..

- FNA biopsy is indicated in patients who present with a solitary suspicious nodule or rapidly enlarging goiter.
- Most patients with thyroid lymphoma have underlying Hashimoto’s thyroiditis.
- MEN 2, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes), Addison’s disease and Down and Turner's syndromes, have a higher incidence.
- These patients should undergo periodic TSH measurements.
Clinical Course

• Some patients with subclinical hypothyroidism → overt hypothyroidism.
• A 20-year follow-up study of patients, initially reported in the Whickham survey, with elevated TSH and positive antibodies but normal thyroxine levels (subclinical hypothyroidism), documented that 55% of female patients became hypothyroid (a progression of 4.3% per year)
• Male patients and those with higher initial TSH levels had an even higher rate of progression
• Patients who had slightly elevated TSH levels but no antibodies did not progress to hypothyroidism
• Rarely, patients may develop Graves‘ disease or lymphoma.
• Thyroid lymphoma has a prevalence 80 times higher than the expected frequency
• Most thyroid lymphomas are of the non-Hodgkin‘s B cell type and tend to occur in older female patients.

Management

• Thyroid hormone replacement therapy is indicated in overtly hypothyroid patients with a goal of normal TSH levels.
• The management of patients with subclinical hypothyroidism (normal T4 and elevated TSH) is controversial.
• Treatment is generally recommended, especially for male patients and those with TSH higher than 10 mU/L.
• Treatment is also indicated in euthyroid patients to shrink large goiters.
• Surgery is occasionally indicated for suspicion of malignancy or for goiters causing compressive symptoms or cosmetic deformity.
Riedel's Thyroiditis

- Riedel's thyroiditis is a rare variant of thyroiditis that was initially described in two patients by Riedel in 1896 and subsequently in a third patient in 1897.
- It is also known as
  - Riedel's struma
  - invasive fibrous thyroiditis
- leads to a wood-like thyroid gland.
- A review of the Mayo Clinic experience disclosed 37 cases in 56,700 thyroidectomies over a 64-year period.
ETIOLOGY AND PATHOGENESIS

• Riedel's thyroiditis is characterized by the replacement of thyroid parenchyma by fibrous tissue, which also invades into adjacent tissues
• Etiology → controversial
• Reported to occur in patients with other autoimmune diseases (eg pernicious anemia, Graves' disease)
• presence of lymphoid infiltration and response to steroid therapy → suggest a primary autoimmune etiology
• Associated with other focal sclerosing syndromes, including mediastinal, retroperitoneal, peri-orbital, and retro-orbital fibrosis and sclerosing cholangitis, suggesting that it may be a primary fibrotic disorder.
HISTOLOGIC FEATURES

- Histologic criteria for the diagnosis of Riedel's thyroiditis were first described by Woolner and coworkers in 1957.
- Fibrotic process consisting of fibroblasts and collagen.
- Microscopic features distinguished from Hashimoto's thyroiditis are:
  - (1) extension of the fibrotic process through the strap muscles and other surrounding tissue,
  - (2) phlebitis with luminal distention by fibrous or lymphoid tissue, and
  - (3) relatively normal remnant thyroid tissue.
- Tissue eosinophil infiltration is also a characteristic finding in fibrous thyroiditis.

Residual follicle, surrounded by lymphocytes, in a sea of fibrotic tissue.
CLINICAL FEATURES

• The disease occurs predominantly in women (male-female ratio, 1:3) between the ages of 30 and 60 years.
• Typically presents as a painless, hard anterior neck mass that progresses over weeks to years to produce symptoms of compression including dysphagia, dyspnea, choking, and hoarseness.
• Patients may present with symptoms of hypothyroidism as the gland is replaced by fibrous tissue.
• Extension of the process can also lead to hypoparathyroidism and, rarely, vocal cord paralysis.
• Physical examination reveals a hard, "woody" thyroid gland with fixation to surrounding tissues.
• Typically, the thyroid is diffusely involved, although unilobular disease has been described.
Diagnosis & Management

• DIAGNOSTIC STUDIES
• An elevated TSH and hypocalcemia may be present in patients with hypothyroidism and hypoparathyroidism, respectively
• Antithyroid antibodies and a mild eosinophilia may be present
• Confirmed by open thyroid biopsy, which also helps exclude carcinoma
• Firm and fibrous gland renders FNA inadequate
TREATMENT

• Surgery is the mainstay of the treatment of Riedel's thyroiditis
• Chief goal of operation → decompress the trachea by wedge excision of the thyroid isthmus and to make a tissue diagnosis
• More extensive resections are not advised owing to the infiltrative nature of the fibrotic process that obscures usual landmarks and structures (recurrent laryngeal nerves, parathyroids, carotid arteries)
• Hypothyroid patients are treated with thyroid hormone replacement
• External-beam radiation therapy is not usually effective
• Some patients remain symptomatic even after these treatment modalities.
• These patients have been reported to experience dramatic improvement after treatment with corticosteroids.
• In another study, relief of symptoms after several weeks of treatment with the antiestrogen medication tamoxifen (20 mg twice a daily).
• Although estrogen receptors have been identified in normal and neoplastic thyroid tissue, tumors from these patients were not positive for estrogen, and the mechanism underlying the response to tamoxifen has been postulated to be related to transforming growth factor (TGF)-beta1.
• TGF-beta1 is a potent growth inhibitor of immature fibroblasts and epithelial cells and has been shown to be upregulated by tamoxifen.
Drug-Induced Thyroiditis

• Several drugs have been reported to cause a drug-induced thyroiditis
• In addition, Lithium has been reported to cause a non-destructive thyroiditis, similar to sporadic silent thyroiditis
• Clinical course similar to the other forms of destructive thyroiditis
• May also develop subacute, sporadic, or suppurative thyroiditis, so these diagnoses need to be evaluated
• Thyroid abnormalities usually resolve with discontinuation of the offending drug
### Causes of Drug-Induced Thyroiditis

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<th>Drug</th>
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<tr>
<td>Amiodarone</td>
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<td>Interferon-alfa</td>
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<td>Interleukin-2</td>
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<td>Lithium</td>
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<td>Minocycline</td>
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• Amiodarone produces thyrotoxicosis by two forms:
  –  (1) iodine-induced hyperthyroidism (type I)
  –  (2) destructive thyroiditis (type II).
• Distinguishing between the two forms - diagnostic dilemma
• Occasionally both forms may be present in the same patient.
• **Type II amiodarone-induced thyrotoxicosis**
  – In general, occurs in a previously normal thyroid,
  – 24 RAIU is completely suppressed
  – Doppler ultrasonography shows absent vascularity.
  – Usually responds to high doses of prednisone (40 to 60mg daily)
• In all cases of amiodarone-induced thyrotoxicosis, the drug should be discontinued if at all possible.
• **Interferon-alpha**
• Up to 70% of patients will develop high serum thyroid peroxidase antibody concentrations
• Two forms of interferon-induced thyrotoxicosis:
  – (1) a Graves’-like hyperthyroidism
  – (2) a destructive thyroiditis
• Frequently mild
• Symptomatic therapy is often all that is necessary.
• Drug usually can be continued to finish the course of therapy
• Thyroid function usually normalizes after the interferon is stopped;
• Affected patients are at increased risk for autoimmune thyroid dysfunction in the future.
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<th>Subacute</th>
<th>Acute suppurative</th>
<th>Riedel’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (years)</td>
<td>All ages, peak 30-50</td>
<td>Painless, all ages, peak 30-40; postpartum and child bearing years</td>
<td>20-60</td>
<td>Children, 20-40</td>
<td>30-60</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>8-9:1</td>
<td>Silent 2:1</td>
<td>5:1</td>
<td>1:1</td>
<td>3-4:1</td>
</tr>
<tr>
<td>Incidence</td>
<td>10% of population at large</td>
<td>Post-partum 2.21% Silent-unknown</td>
<td>Common</td>
<td>Rare</td>
<td>Extremely rare</td>
</tr>
<tr>
<td>Etiology</td>
<td>Autoimmune</td>
<td>Autoimmune</td>
<td>Viral?</td>
<td>Infectious organisms</td>
<td>Unknown</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>Moderate, HLA DR3, DR5, B8</td>
<td>Low</td>
<td>Moderate, HLA Bw-35, DRw8</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Hashimoto’s Pathology</td>
<td>Painless/Post-partum Pathology</td>
<td>Subacute Pathology</td>
<td>Acute suppurative Pathology</td>
<td>Riedel’s Pathology</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
<td>-------------------------------</td>
<td>--------------------</td>
<td>-----------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Prodrome</td>
<td>None</td>
<td>Pregnancy</td>
<td>Viral illness</td>
<td>Viral illness</td>
<td>None</td>
</tr>
<tr>
<td>Goiter</td>
<td>Non-painful, persistent</td>
<td>Non-painful, persistent</td>
<td>Painful, transient</td>
<td>Painful, transient</td>
<td>Non-painful, persistent</td>
</tr>
<tr>
<td>Fever &amp; malaise</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thyroid antibodies</td>
<td>High titer persistent</td>
<td>High titer persistent</td>
<td>Low titer/absent, transient</td>
<td>Absent</td>
<td>Present in majority</td>
</tr>
</tbody>
</table>

In: Surgery of the Thyroid and Parathyroid Glands. Gregory W. Randolph, Ed. 2. p42
<table>
<thead>
<tr>
<th></th>
<th>Hashimoto’s Function</th>
<th>Painless/Post-partum</th>
<th>Subacute</th>
<th>Acute suppurative</th>
<th>Riedel’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid function</td>
<td>Hypothyroid</td>
<td>Thyrotoxicosis is followed by hypothyroidism</td>
<td>Thyrotoxicosis is followed by hypothyroidism</td>
<td>Usually euthyroid</td>
<td>Usually euthyroid</td>
</tr>
<tr>
<td>ESR</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>24-hour RAIU</td>
<td>Variable</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>Normal</td>
<td>Low/normal</td>
</tr>
<tr>
<td>Relapse</td>
<td>Persistent</td>
<td>Common with subsequent pregnancies</td>
<td>Rare</td>
<td>Common, only with left pyriform sinus fistula</td>
<td>Persistent</td>
</tr>
<tr>
<td>Permanent hypothyroidism</td>
<td>Frequent</td>
<td>Common</td>
<td>Occasionally</td>
<td>Rare</td>
<td>Occasionally</td>
</tr>
</tbody>
</table>

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Thank You