A literature review of painful Hashimoto’s thyroiditis: 70 published cases in the past 70 years

**Authors:** Carol Chiung-Hui Peng¹, MD; Rachel Huai-En Chang², MD; Majorie Pennant³, MD; Huei-Kai Huang⁴, MD; Kashif M. Munir³, MD

¹ Department of Internal Medicine, University of Maryland Medical Center Midtown Campus, Baltimore, Maryland, USA
² Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
³ Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine
⁴ Department of Family Medicine, Buddhist Tzu Chi General Hospital, Hualien, Taiwan

**Correspondence:**

Kashif Munir, MD
Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine
Address: 827 Linden Avenue, Baltimore, Maryland, 21201
Phone numbers: 443-552-2960
Fax numbers: 443-552-2991
Email: kmunir@som.umaryland.edu

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Abstract

Painful Hashimoto’s thyroiditis (pHT) is a rare diagnosis and optimal treatment remains unclear. In order to better characterize pHT, Pubmed, Embase, Scopus and Web of Science indexes were searched for case reports or case series reporting painful Hashimoto’s thyroiditis, published between 1951 and February 2019. Seventy cases reported in 24 publications were identified. Female predominance (91.4%) and median age 39.00 (interquartile range 32.50 – 49.75) were observed. Among reported cases, 50.8% had known thyroid disease (including Hashimoto’s thyroiditis, Graves’ disease, and seronegative goiters), 83.3% had positive anti-thyroid peroxidase antibodies, 71.2% had anti-thyroglobulin antibodies. Most cases didn’t have preceding upper respiratory tract symptoms or leukocytosis. Ultrasound features were consistent with Hashimoto’s thyroiditis. Thyroid function at initial presentation was hypothyroid (35.9%), euthyroid (28.1%) or thyrotoxic (35.9%). Cases evolved into hypothyroidism (55.3%) and euthyroidism (44.7%), while none became hyperthyroid after medical treatment. Thyroid size usually decreased after medical treatment. Most cases were empirically treated as subacute thyroiditis with corticosteroids, levothyroxine, or NSAIDS. However, no therapy provided sustained pain resolution. In subgroup analysis, low dose oral prednisone (<25 mg/day) and intrathyroidal corticosteroid injection showed more favorable outcomes. Total thyroidectomy yielded 100% sustained pain resolution. Diagnosis of painful Hashimoto’s
thyroiditis is based on clinical evidence of Hashimoto’s thyroiditis, and recurrent thyroid pain
after medical treatment. The reference standard of diagnosis is pathology. Total
tyroidectomy or intrathyroidal glucocorticoid injection should be considered if low dose
oral prednisone fails to achieve pain control.

**Keywords:** Hashimoto’s thyroiditis, Hashimoto disease, Subacute thyroiditis, Pain

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Introduction

Painful Hashimoto’s thyroiditis (pHT) is a rare variant of Hashimoto’s thyroiditis (HT) that mostly affects women. It is also known as acute exacerbation of HT or painful autoimmune thyroiditis. Diagnosis of pHT is established when painful thyroid presents along with HT, which typically features an elevated serum level of thyroid antibodies (anti-thyroperoxidase [TPO] or anti-thyroglobulin [Tg]) and a firm, painless goiter (1). According to an earlier hypothesis, capsular stretching, which resulted in the rapid enlargement of the thyroid and related pain, may be the cause of pHT (2). However, this hypothesis could not be fully supported because various sizes of the thyroid gland were observed in the reported cases (3). Patients with atrophic thyroid glands were still experiencing pain. The epidemiology and pathophysiology of pHT remain unclear given the limited data from the previous publications.

Among the differential diagnoses of pHT, subacute (or de Quervain’s) thyroiditis, a self-limited disease related to post-viral inflammatory process, is the most common etiology. Other causes include hemorrhagic cyst, suppurative thyroiditis, Riedel’s thyroiditis, infiltrative disease, trauma, or malignant tumor. The majority of patients were initially diagnosed with subacute thyroiditis. However, most patients only had temporary, partial pain relief or did not benefit from medical treatment, including the administration of
corticosteroids and other analgesic medications. A significant number of reported patients experienced repeated relapses that eventually required thyroidectomy to relieve pain effectively (3). However, the appropriate medical treatment for pHT remains unclear.

All the publications regarding pHT are either case reports or case series (4-27), with one short review article (3) available so far. To the best of our knowledge, no statistical analysis for disease characteristics and treatment efficacy has been performed. Therefore, we conducted this first comprehensive review including a total of 24 articles and 70 patients from the literature that met our inclusion criteria. The reviewed publications were published between 1951 and early 2019. This study aimed to provide clinicians the basic demographics, features in clinical presentation, laboratory results, and imaging findings of pHT cases that have been reported in the past 70 years, along with treatment options.

Materials and Methods

Data Sources and Searches

Recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses were adapted in this review (28). The keywords included “pain, painful, Hashimoto’s thyroiditis, Hashimoto’s disease and the controlled vocabularies (i.e., MeSH
A medical research informationist assisted us in performing serial electronic literature searches on databases including PubMed, Embase, Scopus, and Web of Science for English-language research published between 1951 and February 2019.

The search terms used in each database were listed as follows: PubMed: ("Hashimoto Disease"[Mesh] OR "hashimoto thyroiditis" OR "hashimoto disease" OR "hashimoto's" OR "hashimoto"[tiab]) AND ("pain" OR "painful"). Embase: ('Hashimoto disease'/exp OR 'hashimoto thyroiditis' OR 'hashimoto disease' OR 'hashimoto'[tiab]) AND ('pain' OR 'painful'). Scopus: TITLE-ABS-KEY("hashimoto thyroiditis" OR "hashimoto disease" OR "hashimoto's" OR "hashimoto") AND TITLE-ABS-KEY("pain" OR "painful"). Web of Science: TS = ("hashimoto thyroiditis" OR "hashimoto disease" OR "hashimoto's" OR "hashimoto") AND TS= ("pain" OR "painful").

Additional studies also were identified by manual searches of bibliographies from the references in the identified articles. We did not place filters for journal, study design, or subject on the search; however, conference proceedings and abstracts were excluded. The search was last updated on February 14, 2019.
Study Selection

Two authors (CCP and RHC) independently reviewed the study eligibility, and any conflict was resolved by a third author (HKH). We included the studies that identified clinical cases with the presentation of anterior neck or thyroid pain that eventually was clinically or histologically diagnosed as Hashimoto’s thyroiditis. The following studies were excluded in this study: studies with no full text, studies that are not case reports (e.g., original research, discussions, editorials); studies with no final diagnosis of pHT, and studies with cases of typical HT that presented with non-tender neck mass.

Data Extraction

Two authors (CCP, RHC) independently abstracted data from the included articles into a self-designed template using the Cochrane Handbook for Systematic Reviews of Intervention as a reference (29). Study information and clinical characteristics of reported cases were extracted in all studies.

Authors assessed and categorized thyroid function (classified as hypothyroidism, euthyroidism, and thyrotoxicosis) at the initial presentation and during the recovery phase. The interpretation of the status of thyroid function was based on the values provided along with the normal reference values and the authors’ determination described in the report. If
patients appeared euthyroid and were on levothyroxine treatment concurrently, the thyroid function of this patient would be classified as hypothyroid. The characteristics of ultrasound and histology were also documented in the original words of description.

Medical treatments were classified based on the different mechanisms of action of the medications (corticosteroids, nonsteroidal anti-inflammatory drugs [NSAIDs] including aspirin, and levothyroxine). The status of sustained pain resolution was assessed as the treatment outcome. Only patients who received levothyroxine due to pHT without concomitant hypothyroidism at the initial diagnosis were included in this particular analysis. Patients could receive more than one medication simultaneously or serially. If multiple medications were administered simultaneously, the pharmacological outcome of each prescription is unlikely to be identified. Therefore, the treatment outcome was recorded as the overall result from the combination of medications. The route of administration, dosage, and duration of corticosteroid use was further classified. Duration of NSAIDs and levothyroxine was not evaluated due to insufficient information in publications reviewed.

The size of the thyroid gland was compared to that before medical treatment. The time length between the onset of neck pain and surgery was calculated, while surgical type (total thyroidectomy, near-total thyroidectomy, subtotal thyroidectomy, partial thyroidectomy)
and intraoperative findings were documented as described in the original reports. Surgical outcomes were assessed by the status of sustained pain resolution postoperatively, the need for postoperative radioactive iodine ablation, and the relapse rate during the follow-up period. Multiple authors (CCP, RHC, and HKH) evaluated the abstraction accuracy and agreement. Study authors were contacted for additional data or confirmation when needed.

**Data Analysis**

We collected individual-level data from each study. However, not every patient had complete information for each variable. Most of the variables were established into binary data and coded as 1, 0, or not applicable (N/A) or reported into three or more categories. Items that were not mentioned or remained unclear in the case report were assigned N/A, which were not considered in the calculation. Only the overall age of each group were coded as continuous data as shown in Table 1. Age was classified into four ranges based on the distribution to compare the proportion difference between groups. Based on the data reported, countries were categorized into Japan, the United States, the United Kingdom, and other countries to highlight the geographic difference.

We further specified patients who had reported treatment status (Table 1). The patients who had treatment details, including the type of medication, were divided into the medical
group and the surgical group, regardless of their treatment outcome. The medical group comprised patients only receiving medical treatment for pHTh. Regardless of the previous history of medical treatment, patients who eventually underwent thyroidectomy were classified into the surgical group. Further analyses were performed to determine the differences in characteristics between the two groups. Known thyroid diseases were classified as HT, Graves’ disease, and seronegative goiter. Radioactive iodine uptake (RAIU) was categorized into the following three groups: less than 15%, 15% to 30%, and greater than 30%. The vascularity detected by ultrasound was divided into increased or decreased/absence.

The treatment efficacy has been compared between different medications (corticosteroid, NSAIDs, and levothyroxine) and various surgical procedures (total thyroidectomy, near-total thyroidectomy, subtotal thyroidectomy, and partial thyroidectomy) as shown in Table 2. Subgroup analysis of corticosteroid treatment was performed to identify the differences between administration route, dosage, and therapy duration. Given substantial heterogeneity, limited sample size, and insufficient information due to the nature of case reports among the included studies, formal meta-analyses and inferential analysis were not performed. Categorical variables between the two groups were analyzed using the chi-squared test.
In addition to the analysis of patient demographics and disease nature, the number of publications and the overall number of patients were grouped into 10-year increments over 7 decades. For each group, we also analyzed the percentage of patients who underwent thyroid surgery (Table 3).

Results

Study characteristics

There were 1,361 citations identified in our initial database search, and 24 studies eventually met our inclusion criteria (Figure 1). All the included studies were case reports or case series, with the first published in 1957 and the latest one published in 2018. The largest case series consisted of eight patients. There were a total of 70 patients reported in 24 articles. The group who has received medical treatment only comprised 29 patients, and the other group who has undergone surgeries comprised 31 patients, regardless of prior medical treatment status.

Demographics

The baseline characteristics of the patients are shown in Table 1. In general, pHT was
predominantly observed in females (64 cases, 91.4%). The median age was 39 years (interquartile range, 32.50–49.75 years). Among the 70 patients, most were reported in Japan (26 cases, 37.1%), the United States (23 cases, 32.9%), and the United Kingdom (9 cases, 12.9%). The remaining patients were reported by countries in Asia, Europe, and Canada. Ethnicity data were not available in the majority of published studies.

Among the medical and surgical treatment groups, there was no significant difference in the proportion of gender and the distribution of age. The United States accounted for greater than half of the surgical cases that have failed the medical therapy (17 out of 31 cases, 54.8%).

**Number of publications, cases, and surgeries reported based on a time line**

Table 3 summarizes the number of publications, cases, and surgeries from 1951 to 2019. Most cases were reported during 1981–1990 and 2001–2010, with five articles containing 25 patients and six articles containing 20 patients. The majority of thyroid surgeries were performed after 2000, which included 15 cases during 2001–2010 and 10 cases during 2011–2019. The percentage of patients undergoing surgery was 75% during 2001–2010 and 66.7% during 2011–2019. From 1951 to 2000, among the 35 patients, there were only six (17.1%) who underwent surgeries.
**Known thyroid diseases**

There were a total of 37 patients, with 52.8% presenting with known thyroid diseases, including Hashimoto’s thyroiditis, Graves’ disease, and seronegative goiters. No significant differences were observed between the medical and surgical groups regarding known thyroid diseases.

**Symptoms**

Presence of fever was noted in 17 out of 43 patients (60.5%). Only five patients (5/37 cases, 13.5%) reported preceding upper respiratory tract symptoms before developing pHT. The surgical group had a higher percentage of having a fever or a recent history of upper respiratory infection at the first evaluation. Therefore, whether either group had an infection before the thyroiditis is inconclusive in this study.

**Laboratory findings**

The majority of patients did not have leukocytosis (24 out of 27 patients had normal white blood cells counts, 88.9%). Erythrocyte sedimentation rate (ESR) level was reported in 57 patients, while C-reactive protein (CRP) level was reported in 29 patients. Elevated ESR and CRP levels were noted in 35 out of 57 patients (61.4%) and 23 out of 29 patients (79.3%),
respectively. The majority of patients had antithyroid peroxidase (anti-TPO) antibodies (45/54 patients, 83.3%) and anti-Tg antibodies (37/52 patients, 71.2%). A total of 7 patients had both negative anti-TPO and anti-Tg levels. Both titers of anti-TPO and anti-Tg were obtained at the patient’s initial presentation.

**Thyroid function tests**

There were 64 patients with initial thyroid function defined as hypothyroid (23 cases, 35.9%), euthyroid (18 cases, 28.1%), or thyrotoxic (23 cases, 35.9%). Only 38 patients had reported follow-up thyroid function after medical treatment or before surgical treatment. The last reported thyroid function was still categorized into hypothyroidism (21 cases, 55.3%), euthyroidism (17 cases, 44.7%), or thyrotoxicosis (0 case). A higher percentage of patients had eventually developed hypothyroidism, while a case of thyrotoxicosis was not reported after undergoing both treatments.

**Radioactive iodine uptake**

Only half of the cases included in this study have reported a result on RAIU. The majority of patients (19/35, 54.3%) had a low RAIU, defined as uptake less than 15% at 24 hours. There were eight patients (8/35, 22.9%) who had an uptake ratio between 15% and 29% or greater than 30%. For those undergoing RAIU, 6 patients did not report thyroid function, 5 patients
were hypothyroid, 9 patients were euthyroid, and 15 patients were thyrotoxic.

_Ultrasound features_

Only one paper mentioned the use of ultrasound to evaluate pHT before 1987. Only six cases from a few articles reported vascularity with Doppler ultrasound. Heterogeneous hypoechoogenicity with or without intrathyroidal hypoechoic pseudonodules demonstrated in most reported cases is consistent with the characteristic of HT. Increased vascularity was mentioned in 5 cases (83.3%), while the absence of vascularity was noted in 1 case (16.7%).

_Size of the thyroid gland_

Small thyroid gland size before surgery was noted in most patients (21 out of 32 patients had available data on thyroid gland size, 65.6%) after receiving medical treatment. Similar percentages of decreased thyroid gland size were shown for both the medical and surgical groups when repeat measurement was performed at the end of follow-up.

_Treatment methods and responses_

Only 58 cases reported medical therapy, with details included in the analysis. Among the different medications administered in 58 patients, corticosteroids were most commonly administered (42 patients, 72.4%), followed by levothyroxine (26 patients, 44.8%) and
NSAIDs (21 patients, 36.2%) (Table 2). Self-reported pain resolution after the administration of medications was extracted from the articles. Levothyroxine and NSAIDs had lesser pain relief compared to oral corticosteroids according to the percentages of patients’ subjective pain resolution.

A subgroup analysis focusing on corticosteroids, including its route of administration, dosage range, and treatment duration for each episode, was performed (Table 2). Sustained pain resolution was observed in 50% (6 cases) of patients receiving a prednisone dose of less than 25 mg daily, in 25% (2 patients) of patients receiving a prednisone dose of 25–40 mg daily, and in 0% of patients receiving a prednisone dose greater than 40 mg daily. Most patients (13 cases out of all the patients reporting the duration of using corticosteroids, 44.8%) received treatment for 1–3 months. Regarding sustained pain resolution, 50% (3 cases) of patients in the treatment group of less than 1 month and 61.5% (8 cases) of patients in the treatment group of 1–3 months had complete pain resolution.

There were 5 patients who received intrathyroidal corticosteroid injection. In 4 out of 5 patients treated with intrathyroidal injection, triamcinolone acetate 40 mg was administered after oral corticosteroid treatment had failed. In the four patients who achieved sustained pain relief, two patients experienced pain recurrence. In those two patients, one patient
received a total of four local injections and the other received only one local injection before pain permanently resolved.

Besides corticosteroids, NSAIDs, and levothyroxine, Kashyap et al. (23) described one case using acetaminophen, amitriptyline, and gabapentin. However, none of these agents was shown to be effective in pain control.

**Surgery**

Time from pain onset to surgery varies, with a median of 1.5 years (range from 7 weeks to 12 years). A total of 21 patients underwent total thyroidectomy (67.7%), three patients underwent near-total thyroidectomy (9.7%), and six patients underwent subtotal thyroidectomy (19.4%). Only one patient reported by Doniach et al. (4) underwent partial thyroidectomy. However, no treatment response was reported about that patient.

Every patient (100%) achieved complete pain resolution postoperatively in the total thyroidectomy group, while 66.7% (2 patients) of the patients in the near-total thyroidectomy group and 50% (3 patients) of the patients in the subtotal thyroidectomy group achieved complete pain resolution postoperatively. In the subtotal thyroidectomy group comprising six patients, one patient had partial pain relief, and one patient
experienced pain recurrence that was not responsive to postsurgical radioactive iodine ablation for the remnant tissue. Among all the three patient in the near-total thyroidectomy group, one patient developed pain recurrence, which was refractory to radioactive iodine ablation, within 1 year. An eradicative effect of total thyroidectomy in pain relief was observed when comparing subtotal thyroidectomy to total thyroidectomy. No significant difference was noted between total thyroidectomy and near-total thyroidectomy, but comparison between the two is limited due to the small sample size.

In several articles, the intraoperative findings were described (15,18,24). All three cases featured atrophic and firm thyroid glands that had severe adhesion to surrounding tissues. No postoperative complications were reported in any patients undergoing surgical treatment.

**Histopathology**

A total of 59 patients (84.3%) had histopathology reports from specimens obtained either through fine needle aspiration or through surgery. Fine needle aspiration was performed in 43 patients (61.4%). The results revealed a classic picture of Hashimoto’s thyroiditis. The majority of patients presented with diffuse lymphocytic infiltrate, but a few patients only had focal involvement. Varying degrees of fibrosis, from mild fibrotic change to an extensive
degree, were observed, although a greater percentage of patients reported severe fibrosis.

Lee et al. (25) further specified the presence of IgG4 plasma cells in their case. Two patients had pathology-confirmed seronegative pHT.

**Graves’ disease transformation**

One study reported Graves’ disease transformation in four patients (4 out of 70 patients in total, 5.7%) after being diagnosed with pHT from 2 to 7 years (17). Diagnosis of Graves’ disease was established with positive anti-thyrotropin receptor antibody.

**Discussion**

This is a comprehensive review based on case reports and case series to explore the clinical characteristics of pHT, a rare subtype of Hashimoto’s thyroiditis. It may be argued that only cases requiring surgical treatment were reported, while the portion of patients with less severe pain remains unreported. Therefore, by publishing these data with detailed demographic features and analysis of treatment efficacy, we expect that attention will be drawn in pHT from primary care physicians, endocrinologists, and surgeons.

**History of reporting painful Hashimoto’s thyroiditis**

After 2010, the number of publications increased more compared to that in the past
decades, although total reported cases were fewer in number compared with the number of cases reported in the previous decades. It is reasonable since pHT has become better recognized after being introduced and emphasized in the articles published previously. However, the time between initial presentation and surgery was not shortened. After Doniach et al. (4,5) reported the first seven cases of pHT in 1957 and 1960, there was no discussion about pHT for 20 years. It was not until Fui et al. reported one case in 1979 followed by multiple case reports and case series starting from 1986 that the discussion about pHT returned.

Demographics

In our analysis of all the reported patients diagnosed with pHT, sex ratio of females to males was about 10 – 11 : 1, which is close to that of HT with a general sex ratio of 8 – 9 : 1 (1). pHT can develop in any age group, from teenagers to the elderly, but with a peak between 30 and 50 years old, similar to HT (1). Most cases were reported by authors in Japan and the United States. However, due to reporting bias, we are unable to conclude that pHT is more prevalent in these two countries than the other countries.

Clinical presentation

pHT can present with insidious, progressive pain or acute intolerable pain in one lobe or the
whole thyroid. The pain may initially start in one lobe, but it may be felt in the other lobe within days or months (15).

The presence of an atrophic thyroid gland, indicating end-stage thyroid failure, occurs in about 10% of patients with HT (30). Among all the cases that report the size of the thyroid gland at the end of medical treatment or before surgery, a total of 21 patients (65.5%) reported a decrease in size of the thyroid gland in our analysis. The incidence of thyroid atrophy is much higher in patients with pHT than those with HT, which mostly present with goiters (1). The rest of the cases demonstrated fluctuating or remitting clinical course in terms of pain and size of the thyroid gland. The pain may or may not respond to medical treatments. Withdrawal from medications may also be difficult despite their initial promising treatment effect.

Laboratory tests

Due to the likelihood of reporting bias, more than half of the patients (60.5%) were noted to have a fever and elevated ESR (61.4%) and/or elevated CRP (79.3%) levels at initial presentation. However, leukocytosis was not observed in the majority of patients (88.9%). The febrile episodes and elevated ESR and CRP levels could be an indication of inflammatory reaction of thyroiditis itself. Therefore, the presence or absence of fever, leukocytosis, and
elevation of ESR and CRP levels are insufficient to differentiate pHT from subacute thyroiditis.

In our analysis, most patients had either anti-TPO (83.8%) or anti-Tg (72.1%) at initial presentation. Moreover, two patients were diagnosed with seronegative pHT. Presence of antithyroid antibodies is not a diagnostic indicator of Hashimoto’s thyroiditis. In a cohort of 73 patients with painful thyroiditis, 26% of patients had elevated levels of antithyroid antibodies, while only 2 patients were diagnosed with pHT based on final pathology (24).

Initial thyroid function in patients with pHT was either hypothyroid, euthyroid, or thyrotoxic. Thyroid function often fluctuates over time when measured at various stages of thyroiditis. Thyrotoxic patients were not reported during the final thyroid function testing. However, there was no significant difference in the number of hypothyroid or euthyroid patients.

Ipekci et al. provided the trajectory of the change of thyroid function test in a patient who was initially euthyroid, but became thyrotoxic within 1 month, followed by a persistent hypothyroid state after another month (19).

**Ultrasound findings**

The sonographic features of pHT were consistent with Hashimoto’s thyroiditis, which are
characterized by a diffuse heterogeneous hypoechoic pattern. A conclusion based on the size of the thyroid gland could not be formulated on one cross-sectional result because of insufficient baseline data. In patients with HT, the small size of the thyroid gland at baseline may further complicate the interpretation. Therefore, these assessments should be considered with caution. Onoda et al. described the dynamic change of thyroid blood flow under ultrasound during the clinical course of pHT (18). Increased thyroid blood flow to hypoechoic lesions was noted during acute exacerbation, which decreased after medical treatment.

**Diagnosis**

Table 4 lists the comparisons between pHT and subacute thyroiditis (1). We acknowledge that the reference standard of diagnosis is pathology.

**Medical treatment**

No oral medications are able to provide good sustained pain resolution. Oral corticosteroids, mainly prednisone, were widely used for the treatment of pHT. Most cases of subacute thyroiditis were initially treated with oral corticosteroids or NSAIDs. However, pHT poorly responds to oral corticosteroids, regardless of administering a higher dosage of corticosteroids or increasing its treatment duration. Corticosteroid treatment did not
produce satisfactory pain resolution in either group. Only 25% – 50% of patients had reported pain resolution, which indicated that 50% – 75% of patients still experienced neck pain despite the administration of corticosteroids. Development of Cushing’s syndrome after prolonged high-dose corticosteroid use was occasionally reported (13). NSAIDs also failed to provide sustained pain control in most patients with pHT. Levothyroxine use in the absence of hypothyroidism was mostly reported in cases published before 2010. The response rate with sustained pain relief was 34.6%, similar to oral corticosteroids, which yielded a 33.3% response. Short-term use of levothyroxine at TSH-suppressing doses in patients with HT can decrease the size of the thyroid gland (31). However, the thyroid gland size had no effect in the level of pain in patients with pHT.

It is difficult to conclude whether any difference is observed in sustained pain resolution between oral or intrathyroidal injection due to overall small sample size of the injection group. Intrathyroidal corticosteroid injections were first reported in 1974 (32). Ishihara et al. (9) and Paja et al. (27) administered intrathyroidal steroid injections, with triamcinolone 40 mg, in five patients. It resulted in a highly successful rate in pain resolution. However, repeated local injections may be required to completely resolve thyroid pain. From a cytological standpoint, Ishihara et al. described looser arrangement of collagen fibers with edematous inflammation in tender areas of the thyroid, which resolved rapidly after local
corticosteroid injection (33). Similarly, the administration of local injection with
dexamethasone for 3 months along with medical treatment was proven to prevent relapse
of Graves’ disease in a randomized controlled trial containing 191 patients, indicating the
potential role of intrathyroidal corticosteroids in managing inflammation. None of the
patients developed Cushing’s syndrome or overt systemic side effects (34).

**Surgery**

Interestingly, a number of thyroidectomy on patients with pHT increased after the year
2000. Total thyroidectomy was performed in patients with refractory pain after medical
treatment. Total thyroidectomy successfully achieved complete pain relief without
recurrence, while some patients who underwent subtotal or near-total thyroidectomy still
had a relapse of pain. Unfortunately, no rationale was provided in patients who did not
undergo total thyroidectomy. Recently, a randomized controlled trial has reported that total
thyroidectomy improved the quality of life and fatigue of patients diagnosed with HT (35).
This study is only applicable to a subgroup of patients with histologically confirmed HT, with
severe symptoms persisting despite being euthyroid on optimal medical treatment. The
placebo effect and limited follow-up length of 18 months could possibly confound the study
result.
Due to varying levels of fibrotic tissue, successful complete surgical resection required experienced and skillful surgeons (15,18,24). Despite the challenging nature of surgery for patients with pHT, postoperative complications, including laryngeal nerve injury and parathyroid gland damage, were not noted.

**Follow-up**

Among all the 70 patients, only 28 patients (40%) reported duration of follow-up. The relapse of pain occurred within several weeks or up to several years. Short follow-up of less than 1 year may not accurately detect long-term disease recurrence.

**Pathophysiology**

The cause of pain in patients with pHT was previously proposed as capsular stretching due to rapid enlargement of the thyroid (2). However, the reason why patients still experience pain even if the size of the thyroid gland is the same or even if the thyroid becomes atrophic is not clarified yet. Thus, the mechanism of developing pain from pHT remains unknown.

A description of IgG4-positive thyroiditis characterized by rapid progression and higher level of antithyroid antibodies was created by Li et al. in 2009 (36). This report was followed by several other reports reporting this new subtype of autoimmune thyroiditis (25,37,38). Li et
al. retrospectively investigated thyroid specimens from patients who were diagnosed with HT prior to thyroidectomy. Confirmatory diagnosis can only be established by pathology, which was defined as greater than 20 IgG4-positive plasma cells per high-power field and IgG4:IgG ratio greater than 30%. Histologically, a higher grade of fibrosis, pronounced infiltration of the lymphocytes and plasma cells, and follicular cell degeneration are observed in IgG4-positive and non-IgG4-positive thyroiditis. There was no significant difference in pain observed between patients with IgG4-positive and non-IgG4-positive thyroiditis, but comparisons were limited due to a small sample size (37). Although it was reported that IgG4-positive thyroiditis responded well to corticosteroid treatment, there were still patients who underwent thyroidectomy due to pain (25,37). In our analysis, thyroid specimens revealed various degrees of fibrotic change, but majority of the patients reported advanced fibrosis. It may be likely that IgG4 prevalence is more common than is presumed, but insufficient test limits the diagnosis.

**Limitations and strengths**

All the articles included in this systematic review are case reports and case series. There are no randomized controlled trials or cohort studies of pHT in this study. This review is subject to selection and reporting biases from the observational results reported in the publications evaluated. Although there are a total of 70 reported cases, we were unable to include every
case into our subgroup analyses given the lack of data for many of the studied parameters.

The period of the included publications was approximately 70 years, which resulted in significant discrepancies in diagnostic tests, treatment methods, and description of cases. However, the limitations also could be considered a strength in our study. By reviewing the historical data in the past 70 years, we were able to learn the history of this rare and mysterious disease. Despite the limitation in data collection, the heterogeneity of reported cases enabled the understanding of basic patient characteristics and treatment options for pHT.

**Implications for practice and research**

The diagnosis of pHT is based on clinical evidence of Hashimoto’s thyroiditis, including clinical presentation, thyroid function testing, thyroid autoantibodies, ultrasound features, and even histologic findings, along with recurrent or persistent thyroid pain after medical treatment. The reference standard of diagnosis is pathology. Differentiating pHT from subacute thyroiditis remains challenging upon the initial presentation of pain, given that both have a high percentage of fever and elevated levels of ESR and CRP. Therefore, empiric treatment for subacute thyroiditis, including NSAIDs or salicylates for mild pain and high-dose oral prednisone 40 mg daily tapered over 4–6 weeks for severe pain, is often initiated (1). If pain is not relieved after initiating prednisone therapy, a diagnosis of pHT or
suppurative thyroiditis should be considered. Doppler ultrasound may aid in the diagnosis, but radioiodine or technetium imaging study has limited value in the differential diagnosis.

Table 2 summarized the different medications and dosages that have been used in treating pHT, along with the treatment outcome. Based on the results, treatment options include administering low-dose oral prednisone, less than 25 mg/day, for up to 3 months as first-line treatment for patients with pHT. If pain persists or recurs, an intrathyroidal steroid injection of 40 mg triamcinolone acetate can be considered; however, more studies are needed to determine its overall efficacy. Follow-up duration should be greater than 1 year. Total thyroidectomy should be considered in patients with relapse or insufficient pain relief by medical treatment. Surgery should be performed by experienced surgeons to avoid postoperative complications given the severe adhesion of the thyroid gland to surrounding tissues.

Further trials of intrathyroidal injection of corticosteroids will provide more evidence on its use. If possible, immunostaining of IgG subclass of the thyroid specimens from patients with pHT may help in classifying Hashimoto’s thyroiditis. Further research in immunology and biomarkers is of paramount importance to help in understanding the pathophysiology of pHT so that targeted therapy may be developed to resolve pain. Publications of cases with
less severe pain or with favorable outcomes after medical treatment should be encouraged so that treatment options can be formulated.

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Author Disclosure Statement

No competing financial interests exist.

Figure Legend

Figure 1. Identification of eligible studies for analysis.
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Figure 1

Records identified through database searching (n=1,356)
- Medline (Pubmed) (n=150)
- Scopus (n=488)
- Embase (n=614)
- Web of Science (n=104)

Additional records identified through other sources (n=5)

Records identified (n=1,361)

Records after duplicates removed (n=730)

Excluded by title and abstract (n=679)

Duplicated records excluded (n=631)

Full-text articles assessed for eligibility (n=51)

Articles excluded (n=27):
- 11: Wrong patient population
- 7: Full text not available
- 5: Full text in foreign language
- 2: No valuable data to extract
- 2: Not a case report

Studies included in qualitative synthesis (n=24)

Studies included in scoping review (n=24)
Table 1. Characteristics of the patients and treatments

| Characteristics          | No. of Overall Cases | No. of Cases with Reported Treatment Status | Medical Treatment Alone | Surgery |
|--------------------------|----------------------|--------------------------------------------|-------------------------|---------|
|                          |                      | No. of cases / Overall Reported No. (%)    | No. of cases / Total reported Case No. (%) | No. of cases / Total reported Case No. (%) |
| Overall                  | 70                   | 60                                         | 29                      | 31      |
| Gender                   |                      |                                            |                         |         |
| Female                   | 64/70 (91.4%)        | 54                                         | 27/29 (93.1%)           | 27/31 (87.1%) |
| Male                     | 6/70 (8.6%)          | 6                                          | 2/29 (6.9%)             | 4/31 (12.9%) |
| Age                      |                      | Median (IQR)                               | 39 (37, 48)             | 35 (23, 48) |
| Country                  |                      |                                            |                         |         |
| Japan                    | 26/70 (37.1%)        | 18                                         | 11/29 (37.9%)           | 7/31 (22.6%) |
| United States            | 23/70 (32.9%)        | 23                                         | 6/29 (20.7%)            | 17/31 (54.8%) |
| United Kingdom           | 9/70 (12.9%)         | 8                                          | 6/29 (20.7%)            | 2/31 (6.5%) |
| Other                    | 12/70 (17.1%)        | 11                                         | 6/29 (20.7%)            | 5/31 (16.1%) |
| Known thyroid disease    |                      |                                            |                         |         |
| Total                    | 37/70 (52.8%)        | 31                                         | 11                      | 20      |
| Hashimoto’s thyroiditis  | 23/37 (62.2%)        | 22                                         | 9/11 (81.8%)            | 13/20 (65.0%) |
| Graves’ disease          | 5/37 (13.5%)         | 3                                          | 0/11                    | 3/20 (15.0%) |
| Seronegative goiter      | 9/37 (24.3%)         | 6                                          | 2/11 (18.2%)            | 4/20 (20.0%) |
| Fever                    | 17/43 (39.5%)        | 11                                         | 4/19 (21.1%)            | 7/15 (46.7%) |
| Recent history of URI    | 5/37 (13.5%)         | 4                                          | 2/20 (10.0%)            | 2/9 (22.2%) |
| Leukocytosis             | 3/27 (11.1%)         | 3                                          | 2/11 (18.2%)            | 1/8 (12.5%) |
| Elevated ESR level       | 35/57 (61.4%)        | 26                                         | 17/27 (63.0%)           | 9/21 (42.9%) |
| Elevated CRP level       | 23/29 (79.3%)        | 16                                         | 9/11 (81.8%)            | 7/10 (70.0%) |
| Positive Anti-TPO at initial presentation | 45/54 (83.3%) | 37                 | 16/21 (76.2%) | 21/23 (91.3%) |
| Presence Anti-Tg at initial presentation | 37/52 (71.2%) | 31                 | 13/21 (61.9%) | 18/21 (85.7%) |
| Initial thyroid function† |                      |                                            |                         |         |
| Hypothyroidism           | 23/64 (35.9%)        | 23                                         | 9/28 (32.1%)            | 14/35 (40.0%) |
| Euthyroidism             | 18/64 (28.1%)        | 17                                         | 10/28 (35.7%)           | 7/35 (20.0%) |
| Thyrotoxicosis           | 23/64 (35.9%)        | 23                                         | 9/28 (32.1%)            | 14/35 (40.0%) |
| RAIU (uptake at 24 hr)   | < 15%                | 19/35 (54.3%)                             | 8/14 (57.1%)            | 3/13 (23.1%) |
|                          |                      |                                           |                         |         |
|        | 15 – 30% | 8/35 (22.9%) | 8 | 3/14 (21.4%) | 5/13 (38.5%) |
|--------|----------|--------------|---|---------------|--------------|
|        | > 30%    | 8/35 (22.9%) | 8 | 3/14 (21.4%) | 5/13 (38.5%) |
| Ultrasound Showed | 5/6 (83.3%) | 5 | 2/3 (66.7%) | 3/3 (100%) |

**Increased Vascularity**

**Last thyroid function after treatment**

|        | Hypothyroidism | 21/38 (55.3%) | 21 | 10/19 (52.6%) | 5/10 (50.0%) |
|--------|----------------|---------------|----|---------------|--------------|
| Euthyroidism | 17/38 (44.7%) | 14 | 9/19 (47.4%) | 5/10 (50.0%) |
| Thyrotoxicosis | 0              | 0 | 0/19 | 0/10 |

**Decreased Size of thyroid at the end of follow-up**

|        | 21/32 (65.6%) | 18 | 8/12 (66.7%) | 10/12 (83.3%) |

URI, upper respiratory tract infection; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; anti-Tg, anti-thyroglobulin; anti-TPO, anti-thyroid peroxidase; RAIU, radioactive iodine uptake.

Plus–minus values are means ± SD. A total of 100% may not be achieved because values were rounded off.

†If patients appeared euthyroid but on levothyroxine treatment, those are classified as having hypothyroidism. Patients who were on antithyroid medications were classified as having thyrotoxicosis.
### Table 2. Treatment efficacy

| Subgroup | Received Therapy | Sustained pain resolution |
|----------|------------------|---------------------------|
|          | No. of Cases / Total No. (%) | No. of Cases / Total No. Received therapy (%) |
| **Drug** |                  |                           |
| Corticosteroids | 42/58 (72.4%) | 14/42 (33.33%) |
| **Route of administration** |                  |                           |
| Intrathyroidal injection* | 5/42 (11.9%) | 4/5 (80.0%) |
| Oral | 41/42 (97.6%) | 12/41 (29.3%) |
| **Dosage of oral prednisone** |                  |                           |
| < 25 mg/day | 12/23 (52.2%) | 6/12 (50.0%) |
| 25 – 40 mg/day | 8/23 (34.8%) | 2/8 (25.0%) |
| > 40 mg/day | 3/23 (13.0%) | 0/3 (0.0%) |
| **Duration for each episode** |                  |                           |
| < 1 month | 6/29 (20.7%) | 3/6 (50.0%) |
| 1 – 3 months | 13/29 (44.8%) | 8/13 (61.5%) |
| > 3 months | 10/29 (34.5%) | 1/10 (10.0%) |
| **CRP level** |                  |                           |
| CRP elevated | 13/17 (76.5%) | 4/13 (30.8%) |
| CRP within normal limit | 4/17 (23.5%) | 1/4 (25.0%) |
| **ESR level** |                  |                           |
| ESR elevated | 16/33 (48.5%) | 8/16 (50.0%) |
| ESR within normal limit | 17/33 (51.5%) | 5/17 (29.4%) |
| **NSAIDS** |                  |                           |
| 21/58 (36.2%) | 4/21 (19.0%) |
| **Levothyroxine†** |                  |                           |
| 26/58 (44.8%) | 9/26 (34.6%) |
| **Surgery‡** |                  |                           |
| Total thyroidectomy | 21/31 (67.7%) | 21/21 (100%) |
| Near total thyroidectomy | 3/31 (9.7%) | 2/3 (66.7%) |
| Subtotal thyroidectomy | 6/31 (19.4%) | 3/6 (50.0%) |
| Partial thyroidectomy | 1/31 (3.2%) | Unknown |

This efficacy analysis shows patients who received treatment that yield sustained pain relief.

*4 cases had preceding treatment with oral corticosteroids

†Administration of levothyroxine in patients without hypothyroidism at the time of initial diagnosis
With or without prior medical treatment

ESR, erythrocyte sedimentation rate, CRP, C-reactive protein; NSAIDs, nonsteroidal anti-inflammatory drugs
Table 3. Analysis based on time line

| Time Period       | Numbers of publications | Numbers of patients | Numbers of thyroid surgery / Total patients (%) |
|-------------------|-------------------------|---------------------|-----------------------------------------------|
| 1951 - 1960       | 2                       | 7                   | 2/7 (28.6)                                    |
| 1961 - 1970       | 0                       | 0                   | 0/0 (0)                                       |
| 1971 - 1980       | 1                       | 2                   | 0/2 (0)                                       |
| 1981 - 1990       | 5                       | 25                  | 3/25 (12.0)                                   |
| 1991 – 2000       | 1                       | 1                   | 1/1                                           |
| 2001 - 2010       | 6                       | 20                  | 15/20 (75)                                    |
| 2011 - 2019       | 9                       | 15                  | 10/15 (66.7)                                  |
|                            | Painful Hashimoto’s thyroiditis             | Subacute thyroiditis                  |
|---------------------------|--------------------------------------------|---------------------------------------|
| Age at onset (yr)         | All age, peak 30 - 50                       | 20 - 60                               |
| Sex ratio (F:M)           | 10 – 11 : 1                                 | 5 : 1                                 |
| Mechanism                 | Unknown                                    | Unknown, likely related to viral infection |
| Prior viral infection     | Rare                                       | Usual                                |
| Fever                     | Usual                                      | Usual                                |
| ESR/CRP                   | Usually elevated                           | Marked elevated                      |
| Leukocyte count           | Usually normal                             | Normal or slightly elevated          |
| Prior thyroid disease     | Usual                                      | Rare                                 |
| Anti-thyroid antibodies   | Present                                    | Usually absent                       |
| 24-Hour radioactive iodine uptake | Variable*                              | < 5%                                 |
| Thyroid function at onset | Variable*                                  | Usually thyrotoxicosis               |
| Thyroid function in recovery | Variable*                              | Usually euthyroid                    |
| Sonography features       | Diffuse heterogeneous hypoechoic pattern. Increased or absent vascular flow to hypoechoic lesions if present | Diffusely hypoechoic with decreased blood flow to ill-defined hypoechoic thyroid lesions |
| Pathological findings     | Lymphocytic infiltration, germinal centers, Hürthle cells and variable degree of fibrosis. May positive of IgG4 | Non-caseating granulomas, neutrophils and giant cells |
| Respond to corticosteroids or NSAIDS | Poor                                      | Good                                 |

*Variable stands for any possible results, from low, normal, to high compared to the reference range