Case Report

# REVERSIBILITY OF FIBROTIC APPEARANCE OF LUNGS WITH THYROXINE REPLACEMENT THERAPY IN PATIENTS WITH SEVERE HYPOTHYROIDISM

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## ABSTRACT

***Objective:*** To present 2 cases of hypothyroidism with hypoxia associated with computed tomographic (CT) features suggestive of pulmonary fibrosis that resolved with correction of the hypothyroidism.

***Methods:*** Clinical case histories are described, comparative radiologic pulmonary images before and after treatment are provided, and the pertinent literature regarding possible pathologic mechanisms is reviewed.

***Results:*** Our first patient, a 68-year-old woman, presented with symptomatic severe hypothyroidism associated with respiratory failure. A CT scan of her lungs showed appearances suggestive of pulmonary fibrosis. Replacement therapy with levothyroxine led to correction of hypoxia and radiologic abnormalities. Our second patient, a 26-year-old man, presented with symptoms suggestive of obstructive sleep apnea that persisted despite use of positive pressure ventilation. Biochemical evaluation revealed severe hypothyroidism, and a CT scan disclosed pulmonary appearances consistent with fibrosis. His symptoms and radiologic abnormalities also improved after correction of hypothyroidism with levothyroxine therapy.

***Conclusion:*** Radiologic pulmonary abnormalities suggestive of fibrotic disease are associated with severe hypothyroidism. Invasive investigations such as lung biopsy should be deferred until the clinical and radiologic responses to thyroxine replacement therapy have been assessed. **(Endocr Pract. 2009;15:720-724)**

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**Abbreviations:**
**CT** = computed tomographic; **TSH** = thyroid-stimulating hormone

## INTRODUCTION

Hypothyroidism is a common medical condition (1,2), but early diagnosis and treatment have reduced the incidence of severe forms of this disease (myxedema) (3). Nevertheless, severe hypothyroidism is fatal when untreated, especially when manifesting with respiratory involvement (3,4).

Respiratory failure is common in patients with severe hypothyroidism (5) and is associated with high mortality (3). Several pathologic mechanisms have been proposed, including impaired ventilatory responses to hypoxia and hypercapnia (6,7), neuromuscular dysfunction (8,9), central (10) and obstructive sleep apnea (11), reduced diffusion and vital capacity (12), and development of pleural effusions (13). Hypothyroidism causes an accumulation of hyaluronic acid in the dermis and other tissues (14) and thickening of the pharyngeal and laryngeal mucous membranes (12). Although a "process similar to fibrosis affecting the viscera" has long been suspected (15) as a cause for hypoxia in patients with severe hypothyroidism, this has not yet been demonstrated in clinical cases.

We present 2 cases of severe hypothyroidism in conjunction with respiratory compromise and pulmonary radiologic changes that resolved after treatment of the hypothyroidism.

## CASE PRESENTATIONS

### Case 1

A 68-year-old woman with a history of deep vein thrombosis and successful surgical treatment of breast cancer (without radiotherapy) more than a decade earlier presented to our emergency department with a 3-month

history of feeling "slow" in association with deteriorating memory and concentration. She also was concerned about worsening appetite but denied having weight loss. She had noted progressive shortness of breath and was frustrated with her slowed physical actions—"like doing things for the first time." Along with having constipation, she was unsteady on her feet and had had multiple falls. She had stopped smoking many years previously and overall had a 5-pack-year exposure.

Physical examination showed nonpitting edema and fine crepitations at both lung bases with no evidence of cardiac failure. Measurement of arterial blood gases with the patient breathing room air yielded a $Po_2$ of 47.36 mm Hg (6.3 kPa), $Pco_2$ of 28.64 mm Hg (3.81 kPa), and alkalosis with a pH of 7.55, bicarbonate of 25.6 mEq/L (25.6 mmol/L), and base excess of 4.7 mEq/L (4.7 mmol/L). She had anemia with a hemoglobin of 10.1 mg/dL (101 g/L) and a normal neutrophil count. An electrocardiogram revealed low-voltage *P* waves with sinus rhythm.

Although there were no findings suggestive of a respiratory tract infection, intravenous antibiotic therapy was commenced because of a ground-glass appearance on chest radiography. A computed tomographic (CT) pulmonary angiogram excluded the presence of pulmonary embolism but showed findings consistent with bilateral basal fibrosis (Fig. 1 *A*).

The patient failed to respond to antibiotic therapy, with persisting hypoxia and no microbiologic finding of a causative pathogen. Her thyroid function tests showed severe hypothyroidism with a free thyroxine level of 0.54 ng/dL (7.0 pmol/L; reference range, 10 to 30) and thyroid-stimulating hormone (TSH) above measurable limits (>50 mIU/L; reference range, 0.40 to 4.00) with a high titer of anti-thyroid peroxidase antibody (212 IU/mL; reference range, 0 to 100). Levothyroxine therapy was initiated at a dosage of 75 μg daily.

Because hypoxia had persisted for a few days with a $Po_2$ of 56.3 mm Hg (7.5 kPa), a diagnosis of diffuse interstitial fibrosis was considered, and a pulmonary biopsy was planned. The patient, however, had steady improvement with levothyroxine replacement therapy and was weaned off oxygen, with associated improvement in exercise capacity and cognition.

A follow-up CT scan at 4 months showed resolution of lung findings (Fig. 1 *B*), and results of pulmonary function tests at that point were normal (12). With levothyroxine therapy, the patient has remained euthyroid and has had normal oxygen saturations.

### Case 2

A 26-year-old man had a consultation with an otorhinolaryngologist because of recurrent secretory otitis media associated with loud snoring, episodic apnea, tiredness, and somnolence. He was concerned that his relationship was at risk because of his snoring, and his productivity at work was limited by easy fatigability. His medical history was unremarkable except for a previous episode of hepatitis related to gallstones and laparoscopic cholecystectomy.

Examination showed a right middle ear effusion with a mild right hearing loss. He had a body mass index of 29 kg/m$^2$ and scored 8 on the Epworth sleepiness scale (normal score, 6 or less) (16). Oximetry showed changes that were consistent with obstructive sleep apnea. Treatment with continuous positive airway pressure was initiated but was only partially beneficial.

The patient's middle ear effusion persisted, and thyroid function tests were performed as part of subsequent assessment. These studies demonstrated severe hypothyroidism,

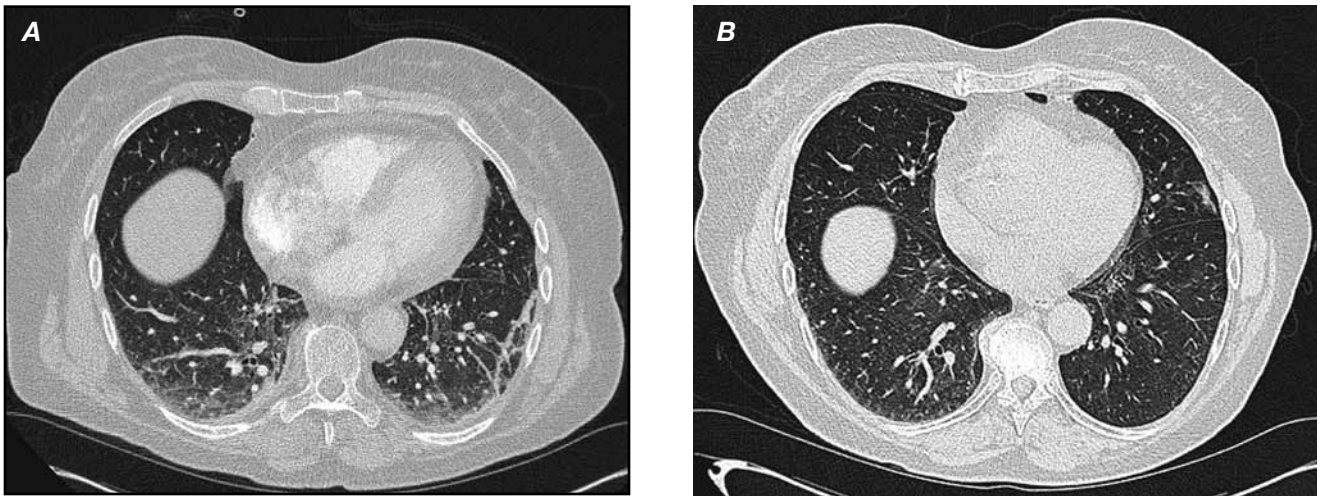


**Fig. 1** (case 1). Computed tomographic images of lung bases before (*A*) and after (*B*) thyroxine replacement in a 68-year-old woman with severe hypothyroidism.

with TSH above the detection limit (75 mIU/L) and free thyroxine below the lower end of the detection limit in conjunction with a high titer of anti-thyroid peroxidase antibody (568 IU/mL; reference range, 0 to 100).

At this point, the patient also had an altered voice, hair loss, poor concentration, shortness of breath, and cold intolerance. Physical examination revealed no signs of infection or cardiac failure. A CT scan of his lungs showed radiologic changes consistent with left basal fibrosis (Fig. 2 *A*).

Treatment was initiated with levothyroxine, beginning with a dosage of 100 μg daily and progressing to 150 μg daily. When the patient underwent reassessment in 4 months, his TSH was 0.26 mIU/L (reference range, 0.40 to 4.00), and a follow-up CT scan of the lungs showed resolution of the abnormalities noted earlier (Fig. 2 *B*). His symptoms diminished with levothyroxine treatment, and he discontinued the use of positive pressure ventilation. At 1-year follow-up, the patient was euthyroid and asymptomatic with use of levothyroxine replacement therapy.

## DISCUSSION

Hypoxia is a common feature of symptomatic hypothyroidism, with the reported incidence up to 69% (5), and numerous pathophysiologic mechanisms have been proposed. The existence of central nervous system abnormalities in myxedema is well established, with decreased cerebral blood flow and glucose consumption (17). Reversible depression of hypoxic ventilatory drive in severe hypothyroidism, leading to alveolar hypothyroidism, has also been demonstrated (7), with reduced chemosensitivity of the respiratory center to hypercapnia being yet another central cause (7). Patients with hypothyroidism, especially women, manifest blunted ventilatory responsiveness to hypercapnia or hypoxia (or both), which is reversible with thyroxine replacement therapy (6).

Weakness of respiratory muscles is another postulated contributor to the hypoxia. This abnormality is thought to be due to a variety of mechanisms, including reversible diaphragmatic dysfunction (18), phrenic nerve involvement (19), and skeletal muscle weakness (20), all of which are reversed with thyroxine replacement therapy. Similarly, substantial improvements in vital capacity, respiratory muscle strength, and transdiaphragmatic pressures have been demonstrated after thyroxine replacement therapy in patients with hypothyroidism (9). Moreover, nerve conduction abnormalities demonstrated in patients with hypothyroidism have been reversible with thyroxine replacement therapy (21).

Hypothyroidism is also associated with both obstructive and central types of sleep apnea (10,11). Thyroxine replacement can diminish apneic episodes and arterial oxygen desaturation, as well as yield improvements in sleep patterns and overall sleep efficiency (22). As our second case illustrates, considerable overlap exists in the clinical manifestations of sleep apnea syndromes and hypothyroidism. Biochemical screening for hypothyroidism is necessary to prevent inadvertent misdiagnosis of hypothyroid sleep-disordered breathing as primary sleep apnea (23).

Since the initial description of myxedema, deposition of mucinous material in the viscera has been considered a part of the pathophysiologic process (15). Histologic analyses have since shown accumulation of hyaluronic acid, leading to the characteristic skin (24) and soft tissue features (12). Deposition of hyaluronic acid also leads to thickening of laryngeal and pharyngeal membranes (12), with a similar histologic finding of hyaluronic acid-rich

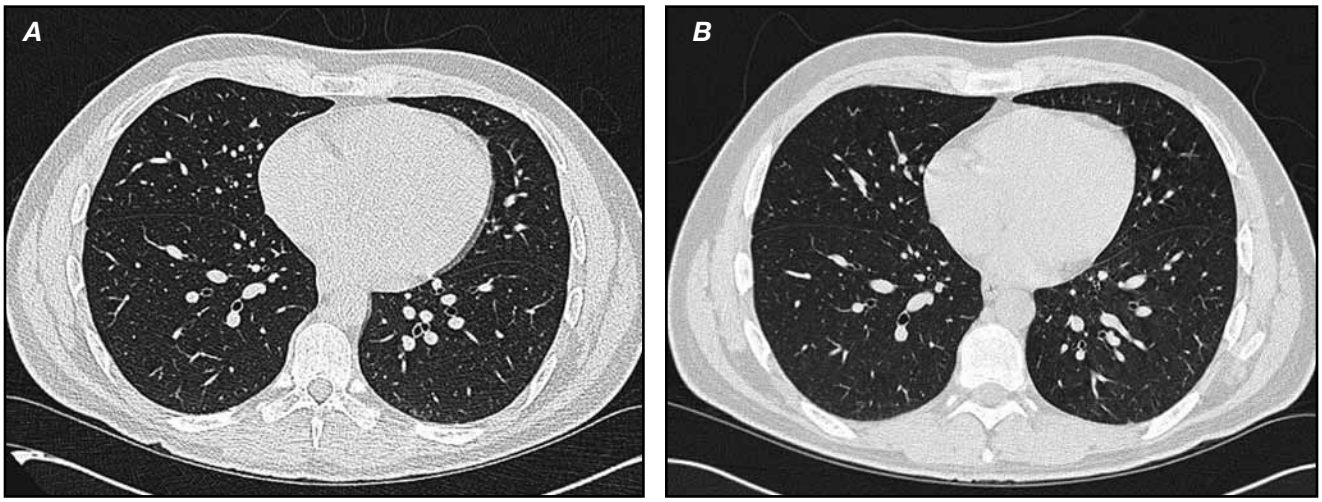


**Fig. 2** (case 2). Computed tomographic images of lung midzones before (*A*) and after (*B*) thyroxine replacement in a 26-year-old man with severe hypothyroidism.

mucopolysaccharides also seen in the bone marrow in severe hypothyroidism (25). Postmortem histologic studies from a virtually untreated patient with severe hypothyroidism showed high concentrations of hyaluronic acid in all tissues except those from the stomach, associated with intracellular edema (26). Interestingly, levothyroxine replacement treatment in hypothyroidism has been shown to induce a significant reduction in accumulation of hyaluronic acid on histologic studies in humans (27) as well as in animal models (28). Fibrous thickening of the alveolar walls of a patient who died with severe hypothyroidism has also been reported (29), possibly with similar pathophysiology. Findings similar to those seen in our patients have also been described in animals with hypothyroidism (30). We postulate that these reversible radiologic changes are likely to be related to pulmonary accumulation of materials such as hyaluronic acid. Although pulmonary biopsy specimens would have been helpful to prove (or disprove) this hypothesis, rapid clinical and radiologic improvement in our patients made such invasive studies clinically unwarranted.

Treatment of such cases of severe hypothyroidism requires thyroid hormone replacement, in conjunction with ventilatory and hemodynamic support, and may necessitate prolonged ventilation (3). With intensive supportive therapy and the early use of levothyroxine therapy, the mortality associated with severe hypothyroidism is declining (4). Apparent pulmonary fibrosis, as described in our patients, should be considered during assessment of patients with hypothyroidism who have radiologic or clinical pulmonary abnormalities. Invasive investigations such as lung biopsy could be deferred until the clinical and radiologic responses to thyroxine replacement have been assessed. We additionally recommend the routine measurement of thyroid hormones in patients with unexplained pulmonary fibrosis, especially if they have symptoms or clinical features suggestive of hypothyroidism.

## CONCLUSION

Respiratory failure in myxedema is multifactorial. Radiologic pulmonary abnormalities similar to those seen in pulmonary fibrosis could be associated with severe hypothyroidism. Invasive investigations such as lung biopsy in patients with hypothyroidism and fibrotic lung changes could be deferred until the response to thyroxine replacement therapy has been assessed.

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## DISCLOSURE

The authors have no multiplicity of interest to disclose.

## REFERENCES

1. **Hollowell JG, Staehling NW, Flanders WD, et al.** Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489-499.
2. **Vanderpump MP, Tunbridge WM, French JM, et al.** The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. *Clin Endocrinol (Oxf)*. 1995;43:55-68.
3. **Behnia M, Clay AS, Farber MO.** Management of myxedematous respiratory failure: review of ventilation and weaning principles. *Am J Med Sci*. 2000;320:368-373.
4. **Jordan RM.** Myxedema coma: pathophysiology, therapy, and factors affecting prognosis. *Med Clin North Am*. 1995;79:185-194.
5. **Yamamoto K, Saito K, Takai T, Yoshida S.** Unusual manifestations in primary hypothyroidism. *Prog Clin Biol Res*. 1983;116:169-187.
6. **Ladenson PW, Goldenheim PD, Ridgway EC.** Prediction and reversal of blunted ventilatory responsiveness in patients with hypothyroidism. *Am J Med*. 1988;84:877-883.
7. **Zwillich CW, Pierson DJ, Hofeldt FD, Lufkin EG, Weil JV.** Ventilatory control in myxedema and hypothyroidism. *N Engl J Med*. 1975;292:662-665.
8. **Duranti R, Gheri RG, Gorini M, et al.** Control of breathing in patients with severe hypothyroidism. *Am J Med*. 1993;95:29-37.
9. **Mier A, Brophy C, Wass JA, Besser GM, Green M.** Reversible respiratory muscle weakness in hyperthyroidism. *Am Rev Respir Dis*. 1989;139:529-533.
10. **Millman RP, Bevilacqua J, Peterson DD, Pack AI.** Central sleep apnea in hypothyroidism. *Am Rev Respir Dis*. 1983;127:504-507.
11. **Rajagopal KR, Abbrecht PH, Derderian SS, et al.** Obstructive sleep apnea in hypothyroidism. *Ann Intern Med*. 1984;101:491-494.
12. **Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds.** *Williams Textbook of Endocrinology*. 11th ed. Philadelphia, PA: Saunders Elsevier, 2008.
13. **Sachdev Y, Hall R.** Effusions into body cavities in hypothyroidism. *Lancet*. 1975;1:564-566.
14. **Smith TJ, Bahn RS, Gorman CA.** Connective tissue, glycosaminoglycans, and diseases of the thyroid. *Endocr Rev*. 1989;10:366-391.
15. Report of a committee of the Clinical Society of London to investigate the subject of myxoedema. London, UK: Longmans, Green & Co. Ltd., 1888.
16. **Johns MW.** A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14:540-545.
17. **Scheinberg P, Stead EA Jr, Brannon ES, Warren JV.** Correlative observations on cerebral metabolism and cardiac output in myxedema. *J Clin Invest*. 1950;29:1139-1146.
18. **Martinez FJ, Bermudez-Gomez M, Celli BR.** Hypothyroidism: a reversible cause of diaphragmatic dysfunction. *Chest*. 1989;96:1059-1063.
19. **Laroche CM, Cairns T, Moxham J, Green M.** Hypothyroidism presenting with respiratory muscle weakness. *Am Rev Respir Dis*. 1988;138:472-474.

20. **Khaleeli AA, Edwards RH.** Effect of treatment on skeletal muscle dysfunction in hypothyroidism. *Clin Sci (Lond)*. 1984;66:63-68.
21. **Lai CL, Liu CK, Tai CT, Lin RT, Howng SL.** A study of central and peripheral nerve conduction in patients with primary hypothyroidism: the effects of thyroxine replacement. *Kaohsiung J Med Sci*. 1998;14:294-302.
22. **Kittle WM, Chaudhary BA.** Sleep apnea and hypothyroidism. *South Med J*. 1988;81:1421-1425.
23. **Skjodt NM, Atkar R, Easton PA.** Screening for hypothyroidism in sleep apnea. *Am J Respir Crit Care Med*. 1999; 160:732-735.
24. **Gianoukakis AG, Jennings TA, King CS, et al.** Hyaluronan accumulation in thyroid tissue: evidence for contributions from epithelial cells and fibroblasts. *Endocrinology*. 2007;148:54-62.
25. **Savage RA, Sipple C.** Marrow myxedema: gelatinous transformation of marrow ground substance in a patient with severe hypothyroidism. *Arch Pathol Lab Med*. 1987; 111:375-377.
26. **Parving HH, Helin G, Garbarsch C, et al.** Acid glycosaminoglycans in myxoedema. *Clin Endocrinol (Oxf)*. 1982; 16:207-210.
27. **Lund P, Hørslev-Petersen K, Helin P, Parving HH.** The effect of l-thyroxine treatment on skin accumulation of acid glycosaminoglycans in primary myxoedema. *Acta Endocrinol (Copenh)*. 1986;113:56-58.
28. **Kofoed JA, Barceló AC.** The acidic glycosaminoglycans in gastric mucosa of athyroid rats: the effects of L-triiodothyronine. *Experientia*. 1978;34:808-809.
29. **Foster M, Barr DP.** Myxedema: record of an autopsied case with special emphasis upon lesions in muscles. *J Clin Endocrinol*. 1944;4:147.
30. **Corcoran BM, Dukes-McEwan J, Rhind S, French A.** Idiopathic pulmonary fibrosis in a Staffordshire bull terrier with hypothyroidism. *J Small Anim Pract*. 1999;40:185-188.