

Pernicious Anemia in Two Cases of Subclinical Hypothyroidism

Jin-Yng, Lu Tien-Shang, Huang
National Taiwan University Hospital
Division of Endocrinology
Department of Internal Medicine

Abstract

The incidence of new cases of pernicious anemia, diagnosed concurrently with the hypothyroidism, has been about 8.5%¹ despite the fact that it was easily missed when ignored by the physician. We now report the occurrence of pernicious anemia with cervical myelopathy and peripheral polyneuropathy in two cases of subclinical hypothyroidism. These will serve as a reminder that, even in the absence of a frank anemic picture, an unexplained cervical myelopathy in patients with thyroid disorders should always alert us to search for underlying pernicious anemia.

Case Report

Case 1: A 33-year-old unmarried woman was diagnosed as having hyperthyroidism about 10 years ago. The initial manifestation was palpitation, hand tremor and diffuse goiter. She had a partial thyroidectomy in 1994 and then maintained in euthyroid status during the next several years without

receiving any medical treatment. About 2 months prior to admission, she began to suffer from bilateral feet and toe numbness followed by symmetrical weakness in both legs. She began to feel abdominal fullness and tightness below the level of the umbilicus that was also associated with difficult stool passage several weeks later. Gradual yellowish discoloration of her skin was also noted. About 2 days before admission, the fullness and numbness ascended to the level of her xyphoid process. She visited our emergency service on August 19, 1999 because of progressive weakness in both legs, making it very difficult for her to stand and walk. She also had difficult voiding for several days. On examination, her consciousness was clear and she was anxious about her current condition. She appeared chronically ill, her body temperature was 36°C, pulse rate 75 per minute, and respiratory rate 18 per minute. Her blood pressure was 102/65mmHg. Mild alopecia and white hair were noted and she also had pale conjunctiva and lips. Her tongue had a beefy-red color; it was rather smooth and lacked papillae. There was no lymphadenopathy or jugular venous engorgement. Her breathing sounds were clear and her heartbeat was regular with no cardiac murmur. Her abdomen was soft with diffuse paresthesia on palpation. No cyanosis or pitting edema was detected. A neurological examination

revealed normal light reflex and normal cranial nerves. Symmetric decline of muscle power (4/5) and a spastic, scissoring gait were noted during the examination. Also, brisk deep tendon reflexes in her knees and ankles were found. There was hypesthesia to thermal stimuli below the level of the xyphoid process; hypesthesia to light touch and pinprick of both hands in glove distribution was also noted. With her eyes shut, a positive Romberg sign was demonstrable. Impairment of vibratory sensations and proprioceptive sensations were also found. Significant laboratory data were hemoglobin 7.6 g/dl, white cell count 2810 /mm³, platelet count 234,000 /mm³, reticulocyte count 0.97%, MCV 115.3 fl. The patient's hemogram on November 23, 1998 was: white count 3200 /mm³, RBC 3.46 x10⁶ /mm³, hemoglobin 12.6 g/dl, MCV 117 fl, platelet 299,000 /mm³) GOT 67 U/l, GPT 29 U/l, T/D bilirubin was 1.2/0.4 mg/dl, r-GT 16 U/l, BUN 9.8mg/dl, creatinine 0.8 mg/dl, cholesterol 112 mg/dl, triglyceride 81 mg/dl, haptoglobin <5.83 mg/dl (normal 64.81~157.48 mg/dl), vitamin B₁₂ 17.4 pg/ml (normal 200~900 pg/ml, deficiency <100 pg/ml), folic acid 16.4 ng/ml (normal 6~20 ng/ml, deficiency <4 ng/ml). The serum ferritin level was 109 ng/ml (normal 3.0~151 ng/ml), iron 134 µg/dl (normal 66~155 µg/dl), TIBC 230 µg/dl (normal 275~332 µg/dl). The thyroid function tests revealed free

Pernicious Anemia and Subclinical Hypothyroidism

T4 1.01 ng/dl (normal 0.6~1.75 ng/dl), hsTSH 20.6 IU/ml (normal 0.5~5 μ IU/ml). The plasma ACTH was 6.3 pg/ml at 8:00am and 5.6 pg/ml at 4:00pm. The serum cortisol level was 16.54 μ g/ml at 8:00 am, and 4.07 μ g/ml at 4:00pm. The titers of antimicrosomal antibody and antithyroglobulin antibody were not elevated. The gastric parietal antibody was positive. Electromyography and evoked potential studies revealed early signs of sensory neuropathy and a markedly prolonged central conduction time that was consistent with a cervical cord lesion. However, MRI of the spine failed to reveal any abnormal changes in the spinal cord and paraspinal space. A panendoscopic biopsy was performed on August 26, 1999, and the pathology revealed chronic atrophic gastritis with lymphocyte infiltration of the stomach body, with no *Helicobacter* infection. Peripheral blood smear revealed anisocytosis and poikilocytosis, and typical hypersegmentation of white cells. Under the impression of pernicious anemia with cervical myelopathy and peripheral neuropathy, vitamin B₁₂ (Bistin 1000 μ g/amp) 1000 μ g qd intramuscularly had been given for 14 days and then 1000 μ g per week for 8 weeks beginning August 24. She felt improvement in her gait and paresthetic sensation soon after starting the vitamin injections. The maximal reticulocyte count (from baseline 0.97% to 5.72%) was achieved on August

30, the 7th day of treatment. The hemoglobin level increased to 10.7 g/dl on September 15, 11.0 g/dl on September 23 and 13.1 g/dl on October 12, the MCV were 96.3 fl, 93.7fl and 87.2 fl respectively. The Romberg sign became negative and later her unsteady gait disappeared. Due to subclinical hypothyroidism, levothyroxin 50 µg per day was prescribed thereafter.

Case 2: A 48 y/o woman presented in November 1999 having had a gradual onset of numbness and stiffness over her extremities for 3 months. She also experienced tightness and swelling sensation below the xyphoid process that extended down to both feet. She had difficult defecation the previous 10 days but had no problem with urination. She also complained that her hair began turning white when she was about 30 years old. Her past history was unremarkable except that she had been diagnosed as having hyperthyroidism in her early twenties. Physically, her consciousness was clear. Her body temperature was 36.8°C, pulse rate was 82 per minute and respiratory rate 20 per minute. Her blood pressure was 116/67mmHg. Her conjunctiva was not anemic and the sclera was not icteric. She had a beefy-red tongue with a smooth surface that lacked papillae. There was no lymphadenopathy or jugular venous engorgement. A grade I goiter was palpable over the anterior portion of her neck. Neurologically, the cranial nerves were normal. Manual

Pernicious Anemia and Subclinical Hypothyroidism

muscle test revealed good muscle power, but the deep tendon reflex was brisk and increased. Numbness was noted in both hands, the ulnar side of both forearms and the trunk from the xyphoid process down to both feet, with a decrease in pinprick and vibration sensation. The proprioceptive sensation was poor in the toes. The significant laboratory data were as following: hemoglobin 13.3 g/dl, white cell count 5640 /mm³, platelet count 266,000 /mm³, reticulocyte count 1.59%, MCV 118.5. GOT 18 U/l, GPT 19 U/l, T/D bilirubin was 0.9/0.3 mg/dl, r-GT 26 U/l, BUN 15.5 mg/dl, creatinine 0.8 mg/dl, cholesterol 249 mg/dl, triglyceride 190 mg/dl, vitamin B₁₂ 36.5 pg/ml, folic acid 14.7 ng/ml. The thyroid function tests results were free T4 1.0 ng/dl, and hsTSH 12.5 IU/ml. The ACTH was 35.4 pg/ml at 8:00am and the cortisol level was 16.6 μg/ml at 8:00 am. The titers of antimicrobial antibody was >20480x and antithyroglobulin antibody was >1280x. The gastric parietal cell antibody was positive. The spine MRI revealed no evidence of thoracic or cervical spine compression. She was given vitamin B₁₂ 1 mg intramuscularly and thyroxine replacement 50 μg per day beginning November 30, 1999. She subjectively felt both the paresthesia and general discomfort improved after this therapy.

Discussion

Mild anemia is a common feature in hypothyroidism, occurring in about 25% of untreated patients; most of whom are normocytic anemia¹. Macrocytic anemia associated with autoimmune thyroiditis can result from malabsorption of either folate or vitamin B₁₂. As many as 10% of the patients with hypothyroidism, caused by autoimmune thyroiditis, have pernicious anemia^{2,3}. In addition, hypothyroid dyslipidemia can lead to increased membrane lipid content, also causing macrocytosis⁴. White blood cells and platelet counts are usually normal in hypothyroidism; however, if there is coexistent pernicious anemia, as in case one, low cell counts will ensue¹.

Circulating antithyroid antibodies, such as antimicrosomal (AMA) and antithyroglobulin (ATA) antibodies, are usually present in patients with autoimmune thyroid disease⁵. Antimicrosomal antibodies are detectable in more than 90% of the patients with chronic autoimmune thyroid disease, and nearly 100% of the individuals with Hashimoto's thyroiditis and more than 70% of patients with Graves' disease have positive titers⁶. Elevated levels of AMA are frequently noted in various autoimmune diseases, such as lupus erythematosus, rheumatoid arthritis, autoimmune pernicious anemia (PA), Sjogren's syndrome, type 1 diabetes mellitus and Addison's disease^{5,7,8}. About

15% of adults (especially women) in the USA have elevated AMA titers, and the presence of AMA should alert the clinician to the possibility of hypothyroidism. The subclinical hypothyroidism combined with macrocytic anemia in our patient prompted our search for underlying PA.

The human sodium iodide symporter (hNIS), a mediator of the active transport of iodide, has been demonstrated to be present not only in thyroid follicular cells but also in other extrathyroid tissues such as the: salivary gland, lacrimal gland, gastric mucosa, choroids plexus and lactating mammary gland⁹. The antibody to hNIS may contribute to the concurrence of pernicious anemia and autoimmune thyroiditis⁹.

The first description of what may have been PA was credited in 1822¹⁰. In 1849, Addison reported a case of PA¹¹. Since then, several reports had been mentioned¹². Currently, PA is considered to be the most common cause of deficiency in vitamin B₁₂. It is associated with antibodies to parietal cells and their products, gastric mucosal atrophy, achlorhydria, and deficiency of the intrinsic factor (IF), which is necessary for absorption of vitamin B₁₂^{11,12}. The clinical manifestations of PA are attributed to the resultant deficiency of cobalamin. The cobalamin is necessary for effective DNA synthesis in cells. Therefore, the disease affects tissues with a rapid cell turnover, such as the

bone marrow and the mucosa of the gastrointestinal and genitourinary tracts¹³.

The corresponding clinical features include macrocytic anemia, variable degrees of pancytopenia, atrophy of the tongue, gastric mucosa and the small intestine¹². In addition, the disease affects peripheral and central nervous systems and results in polyneuropathy, myelopathy or altered mental status¹⁴.

Dyspnea on exertion, general weakness and palpitation may be present, depending on the rapidity of the onset and severity of the anemia. Our patient (case 1) was completely asymptomatic and yet had severe anemia, this reflected the insidious onset of the anemia, which is not unusual in PA.

The patient may have premature graying or whitening of the hair, vitiligo may also be noted. Glossitis in conjunction with an inability to tolerate any oral intake may be a prominent complaint as the tongue may be painful, beefy-red and devoid of papillae¹⁵, as in this patient. Atrophic gastritis may be confirmed by pathological examination, infiltration of the mucosa with lymphocytes implies a possible immune basis for the pathogenesis of this disorder¹³. The neurologic presentation was the most interesting factor in our patients and included both the central and peripheral nervous systems. Their chief complaints were due to severe neurological involvement even though a spine MRI failed to demonstrate any evidence of a spinal cord lesion.

Paresthesias, increased deep tendon reflexes, long tract signs, impaired proprioception and vibratory senses, memory deficits and psychosis are the commonest findings of PA¹⁴. The pathological changes included demyelination and axonal destruction in the posterior and lateral columns of the spinal cord¹⁴. Patients with PA have an estimated 3~5 times the risk of gastric adenocarcinoma so that regular follow-up is recommended¹².

Serum vitamin B₁₂ levels are usually low in patients with PA. The normal range was 200~900 pg/ml; in patients with PA the vitamin B₁₂ was usually less than 100 pg/ml. However, the vitamin B₁₂ level predicted neither the degree of anemia nor the MCV. In the subgroup of patients who had a vitamin B₁₂ level less than 50 pg/ml, like this patient, the median MCV was 114 fl (79~133). Other laboratory data include evidence of ineffective erythropoiesis, such as an increased lactate dehydrogenase level and indirect hyper-bilirubinemia. The yellowish discoloration of skin was one of this patient's chief complaints, however, since the laboratory data did not reveal hyperbilirubinemia it was then thought to be due to the hypothyroidism. The early recognition and diagnosis of PA necessitates a high degree of clinical suspicion. In our second case, the hemoglobin was still 13.3g/dl, but the macrocytosis was prominent (MCV 118.5). Even though the clinical picture

did not favor anemia, the macrocytosis hinted at presence a vitamin B₁₂ deficiency. This can serve as a reminder for us to check the vitamin level and the gastric parietal antibodies. The anti-parietal cell antibody was positive in more than 90% of the patients with PA; the anti-intrinsic factor antibody was in 60% of the patients¹⁶. The anti-thyroid antibody was also present in about 50% of the patients with PA, even though there was no evidence of hypothyroidism.

The treatment of PA should last a lifetime. The arbitrary recommended dosage of daily injections of 1,000 µg of vitamin B₁₂ for the first week, then weekly injections for the first month followed by monthly injections for the rest of the patient's life. This regimen is commonly used because of the negligible toxicities associated with such therapy^{12,13,15}. Within hours after the initiation of cobalamin therapy, patients may experience a subjective sense of improvement. The bone marrow morphology will revert to normal within 24~48 hours. Reticulocytosis occurs and peaks on the 7th day of treatment. The serum potassium level should be monitored during vitamin B₁₂ supplement since hypokalemia may develop during therapy. A folate-rich diet should be encouraged; folate supplements also can be prescribed. Without vitamin B₁₂, however, folate therapy alone may exacerbate the

neurological abnormalities¹⁷. Hematological abnormalities usually revert to normal within 2 months. Most patients report either a complete (50%) or partial response to treatment; the degree of response depends on the pretreatment severity and duration of the neurologic symptoms. Most of the improvement occurred within the first 6 months of therapy¹.

Our patients presented with a normal T3, T4 and free T4 levels, and yet an elevated TSH, so called “subclinical hypothyroidism”⁴. Overt hypothyroidism usually ensues in these patients. In the elderly, it is unclear whether subclinical hypothyroidism should be treated, because symptoms are usually minimal or absent, there may be no recognizable clinical benefit from treatment, and the risks of overtreatment are great. However, for younger adults like our patients, there seems to be no advantage in allowing a pathologic condition to progress to clinical significance. In addition, the lipid profile usually improves and the patients feel better subjectively after thyroid hormone replacement.

In summary, pernicious anemia with clinical thyroid disorders is rather common in clinical practice. Any patient with an unexplained neurologic deficit, with or without the appearance of anemia¹⁸, should be investigated to determine whether vitamin B₁₂ deficiency and gastric parietal antibody are

present.

References

- 1.Horton L, Coburn RJ, England JM, et al. The hematology of hypothyroidism. *Quart J Med* 1975; 177: 101-24.
- 2.Tudhope GR, Wilson GM. Anemia in hypothyroidism. *Quart J Med* 1960; 29: 513.
- 3.Tudhope GR, Wilson GM. Deficiency of vitamin B12 in hypothyroidism. *Lancet* 1962; 1: 703.
- 4.Carmel R, Spencer CA. Clinical and subclinical thyroid disorders associated with pernicious anemia. *Arch Intern Med* 1982; 142: 1465-9.
- 5.Whittingham S, Youngchaiyud U. Thyrogastric autoimmune disease. *Clin exp immunol* 1975; 19: 289-99.
- 6.Marcocci C, Chiovato L. Thyroid directed antibodies. In: Braverman LE, Utiger RD. Werner and Ingbar's *The Thyroid*: 8th ed. Philadelphia: A.W. Kluwer Co., 2000; 414-31.
- 7.Peltz S, Barchuk W, Oppenheimer J, et al. Chronic angio-edema of the tongue associated with pernicious anemia and Hashimoto's thyroiditis. *Clin Exp Dermatol* 1995; 20: 351-2.
- 8.Krol TC. Myasthenia gravis, pernicious anemia and Hashimoto's thyroiditis. *Arch Neurol* 1979; 36: 594-5.
- 9.Spitzweg C, Joba W, Schriever K, et al. Analysis of human sodium iodide symporter immunoreactivity in human exocrine glands. *J Clin Endocrinol Metab* 1999; 84: 4178-84.
- 10.Combe JS. History of a case of anemia. *Trans Med Chir Soc Edinburgh* 1824; 1: 194-203.
- 11.Castle WB. Development of knowledge concerning the gastric intrinsic factor and its relation to pernicious anemia. *N Engl J Med* 1953; 249: 603-14.
- 12.Toh BH, Jan R, Driel V, et al. Gleeson. Pernicious anemia. *N Engl J Med* 1997; 337: 1441-8
- 13.Pruthi RK, Tefferi A. Pernicious anemia revisited. *Mayo Clin Proc* 1994; 69: 144-50.
- 14.Shevell MI, Rosenblatt DS. The neurology of cobalamin. *Can J Neurol Sci* 1992; 19: 472-86.
- 15.Karnad AB, Agnes KH. Pernicious anemia, early identification to prevent permanent sequelae. *Postgrad Med* 1992; 91: 231-7.
- 16.Stabler SP, Allen RH, Savage DG, et al. Clinical spectrum and diagnosis of cobalamin deficiency. *Blood* 1990; 75: 871.
- 17.Dickinson CJ. Does folic acid harm people with vitamin B12 deficiency? *Q J Med* 1995; 88: 357-64.
- 18.Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamine deficiency in the absence of anemia or macrocytosis. *N Engl J Med* 1988; 318: 1720.

惡性貧血與亞臨床性甲狀腺機能低下

呂金盈 黃天祥

國立台灣大學附設醫院 內科部內分泌科

摘 要

在罹患亞臨床性甲狀腺機能低下的病人中，同時發生初次診斷之惡性貧血的機率，約佔百分之八點五左右。但是在臨床上，此種情況卻相當容易被忽略。在此提出兩個患有亞臨床性甲狀腺機能低下病患，以頸椎脊髓病變及多發性周邊神經病變為主要臨床表現，最後證實為惡性貧血的病例報告。希望能提醒臨床醫師、在甲狀腺機能異常的病人，即使完全沒有貧血的症狀及徵候，對於無法解釋的頸椎脊髓病變，我們仍應想到惡性貧血，或是維他命 B12 缺乏的可能性。