REVIEW ARTICLE

Anemia in thyroid diseases

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ABSTRACT

Anemia is a frequent, although often underestimated, clinical condition accompanying thyroid diseases. Despite the fact that anemia and thyroid dysfunction often occur simultaneously, the causative relationship between the disorders remains ambiguous. Thyroid hormones stimulate the proliferation of erythrocyte precursors both directly and via erythropoietin production enhancement, while iron-deficient anemia negatively influences thyroid hormone status. Thus, different forms of anemia might develop in the course of thyroid dysfunction. Normocytic anemia is the most common, while macrocytic or microcytic anemia occurs less frequently. Anemia in hypothyroidism might result from bone marrow depression, decreased erythropoietin production, comorbid diseases, or concomitant iron, vitamin B_{12}, or folate deficiency. Altered iron metabolism and oxidative stress may contribute to anemia in hyperthyroidism. The risk of anemia in autoimmune thyroid disease (AITD) may be related to pernicious anemia and atrophic gastritis, celiac disease, autoimmune hemolytic syndrome, or rheumatic disorders. The coexistence of anemia and thyroid disease constitutes an important clinical problem. Thus, the aim of this review was to provide a comprehensive summary of data on the prevalence, potential mechanisms, and therapy of anemia in the course of thyroid diseases from the clinical and pathogenetic perspectives. Thyroid dysfunction and AITD should be considered in a differential diagnosis of treatment-resistant or refractory anemia, as well as in the case of increased red blood cell distribution width. Of note, the presence of AITD itself, independently from thyroid hormone status, might affect the hemoglobin level.

Introduction Anemia is a common, although frequently underestimated, clinical condition accompanying thyroid diseases.[1] Despite the fact that anemia and thyroid dysfunction often occur simultaneously, the causative relationship between the disorders remains ambiguous. Different forms of anemia might emerge in the course of thyroid dysfunction. Normocytic anemia is the most common, while microcytic and macrocytic anemias are less prevalent.[2,3]

There are abundant literature data on the association between thyroid status and anemia. However, the available studies often report conflicting results, and there is limited number of large cohort studies. Both anemia and thyroid disease, due to their high prevalence and close interrelation, are significant clinical problems often encountered by practitioners. Therefore, this review aimed to provide a comprehensive summary of data on the prevalence, potential mechanisms, and therapy of anemia in the course of thyroid diseases from the clinical and pathogenetic perspectives.

Epidemiology Both anemia and thyroid dysfunction are common disorders.[4-6] The peak incidence of anemia is around 10% in the female population of child-bearing age, as well as in the elderly population.[7,8] A recent large cohort population-based study demonstrated that in the population at an estimated mean age of 59.4 years, the prevalence of thyroid function disturbances was 5.0%, while anemia was present in 5.9% of the studied patients. In a study by M'Rabet-Bensalah et al,[1] anemia was most frequent in overt hyperthyroidism (14.6%) and was less often observed in overt hypothyroidism (7.7%).[1] Omar et al[9] reported even higher incidence of anemia accompanying hyperthyroidism and hypothyroidism: 40.9% and 57.1%, respectively. Hemoglobin concentrations were reported to be significantly lower both in women with increased and in those with decreased thyroid-stimulating hormone (TSH) levels, when compared with euthyroid women.[10] In fact, in a study on patients with Graves hyperthyroidism, one third of the population presented anemia, while restoration of

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euthyroidism resulted in a significant improvement of hematological status.[11]

The incidence of subclinical thyroid dysfunction, defined as a serum TSH concentration above the upper limit of the reference range when serum free thyroxine and triiodothyronine concentrations are within their reference ranges, increases with age and eventually reaches up to 20% of female patients over 60 years of age.[12] Data on the incidence of anemia in subclinical thyroid dysfunction are inconsistent. According to M'Rabet-Bensalah et al,[1] the incidence of anemia in subclinical hypothyroidism was comparable to that in euthyroid population. However, numerous reports have also linked anemia with subclinical thyroid dysfunction.[13,14] In a study by Erdogan et al,[15] the prevalence of anemia in patients with overt and subclinical hypothyroidism was similar and reached 43% and 39%, respectively. In a prospective study by Christ-Crain et al,[16] performed on a group with subclinical thyroid dysfunction, the restoration of euthyroidism resulted in an increase in erythropoietin concentrations; at the same time, hematocrit and hemoglobin levels did not change significantly.

A large cohort study[17] revealed that, even in euthyroid patients, there is a significant positive relationship between the concentrations of free thyroid hormone and hemoglobin, hematocrit, and erythrocyte count, with a simultaneous negative correlation between TSH levels and the serum iron concentration and transferrin saturation.[17]

Etiopathogenesis Thyroid hormones play a crucial role in hematopoiesis, particularly in erythropoiesis. They exert a direct stimulating effect on the proliferation of erythrocyte precursors, but also promote erythropoiesis by increasing erythropoietin gene expression and erythropoietin production in the kidneys.[18-21] Experimental studies demonstrated an enhanced erythroid colony growth induced by free triiodothyronine.[22] In hypothyroid patients, the number and proliferative activity of erythroid cells in the marrow is reduced.[23] Additionally, gelatinous transformation of the marrow ground substance, characterized by mucopolysaccharide accumulation, was observed in a patient with profound hypothyroidism.[24] Indeed, hypothyroid patients show a decreased plasma concentration of erythropoietin.[23] The observed changes are regarded as physiological adaptations to the reduced oxygen requirement of the tissues, due to the diminished basal metabolic rate in hypothyroidism.

The etiopathogenesis of anemia in hypothyroidism is complex and may be related to depressed bone marrow stimulation, decreased erythropoietin production, nutrient deficiency (including iron, vitamin B_{12}, or folate), as well as comorbid diseases. In patients with autoimmune thyroid disease (AITD), the risk of anemia may be increased by concomitant autoimmune disease such as pernicious anemia and atrophic gastritis, celiac disease, autoimmune hemolytic syndrome, or soft tissue rheumatic disorders.

The mechanism of developing anemia in hyperthyroidism is less clear. In patients with hyperthyroidism, bone marrow erythroid hyperplasia and elevated erythropoietin levels were detected.[23] However, erythrocytosis in blood morphology is rare, probably owing to concomitant iron, vitamin B_{12}, or folate deficiency.[23] Altered iron metabolism, hemolysis, and oxidative stress leading to enhanced osmotic fragility of erythrocytes and lipid peroxidation, resulting in shortened erythrocyte survival, were suggested as the potential causes of anemia in thyrotoxicosis.[1,11,25] On the other hand, anemia, particularly the iron-deficient variant, may adversely affect thyroid hormone status.[26] In fact, iron is vital for the activity of thyroid peroxidase, an iron-containing enzyme that is crucial in the first steps of thyroid hormone synthesis. Experimental studies demonstrated that iron deficiency decreases thyroid peroxidase activity, and therefore may contribute to the depression of thyroid function. The relative risk of hypothyroidism in children with iron-deficiency anemia was found to be 5.5 in overt hypothyroidism and 1.9 in subclinical hypothyroidism, in comparison with nonanemic children. A significant negative correlation between TSH and hemoglobin levels was observed.[26] Therefore, there is a bilateral relationship between anemia and thyroid and metabolic status.

Comorbid conditions and factors contributing to anemia in the course of thyroid diseases **Iron deficiency and microcytic anemia** Iron deficiency is the most common cause of anemia.[27] In the case of iron deficiency, the positive effect of iodine supplementation on thyroid function is abolished.[28] Iron-deficiency anemia in women might be aggravated by hypermenorrhea or menorrhagia, which are some of the clinical manifestations of thyroid hormone deficiency.[29] Furthermore, the pathogenesis of uterine bleeding related to hypothyroidism is multifactorial. TSH may to some extent exert similar effects to those of follicle-stimulating and luteinizing hormones, since they share a common α subunit. It reduces the luteinizing hormone secretion, thus leading to a decrease in the progesterone level and estrogen breakthrough bleeding, secondary to anovulation. In addition, a lower concentration of sex hormone-binding globulin is observed in hypothyroidism. This results in an increase in circulating free estrogen levels, which exerts a proliferative effect on the endometrium. Myxedematous changes in the extracellular matrix surrounding the superficial blood vessels, alterations in platelet and arterial wall prostaglandin production and metabolism, as well as reduced secretion of von Willebrand factor may lead to platelet dysfunction and disturbed primary hemostasis.[30] Severe hypothyroidism may result in acute menorrhagia causing profound and life-threatening anemia.[31] Additionally, occult hypothyroidism was reported as a potential cause of

menometrorrhagia in women with implanted intrauterine device. Bleeding became instantly less abundant following a successful 3-month therapy with L-thyroxine.[32]

An important hematological parameter affected by thyroid hormone status and iron deficiency is red blood cell distribution width (RDW), which reflects the degree of erythrocyte anisocytosis. RDW increases iron-deficiency anemia, but can also be a sign of vitamin B_{12} or folate deficiency. Recent studies have found that RDW is increased in diseases characterized by inflammation, such as hypertension, myocardial infarction, heart failure, inflammatory bowel diseases, or rheumatoid arthritis. Moreover, it was proved to be a predictor of mortality in several conditions.[33] In a study by Dorgalaleh et al,[21] both hyperthyroidism and hypothyroidism were associated with significantly lower mean corpuscular volume (MCV), mean cell hemoglobin, mean corpuscular hemoglobin concentration, and hemoglobin and hematocrit levels, but higher RDW, as compared with euthyroid controls. In a study by Bremner et al,[17] thyroxine concentrations negatively correlated with RDW. In addition, a similar association was observed by Aktas et al,[33] who analyzed hematological parameters in patients with Hashimoto thyroiditis (HT) in comparison with a healthy control group. They observed that patients with HT presented higher RDW values as compared with controls. Thus, the authors indicated that increased RDW in patients without iron deficiency suggests the need to assess the thyroid status, especially in the female population. Montagnana et al[34] observed a positive correlation between RDW and TSH levels, while RDW was significantly higher in patients with hypothyroidism compared with euthyroid controls. In another study, Lippi et al[35] found a positive correlation between the thyroid hormone concentration and the level of anisocytosis in euthyroid elderly patients.

Microcytic anemia has been so far more associated with hyperthyroidism than with other thyroid function states. MCV was significantly lower in hyperthyroid patients, as compared with euthyroid controls.[10,36] Omar et al[9] reported a very high incidence (87.7%) of microcytosis among patients with hyperthyroidism, regardless of the hemoglobin status. Iron deficiency is also often associated with subclinical hypothyroidism, especially in women.[27] In a study by Das et al,[2] performed in Indian population with hypothyroidism, microcytic anemia was the second most prevalent type of anemia (following normocytic normochromic anemia) with a prevalence of 43.3%.[2] In a study by Nekrasova et al,[13] subclinical hypothyroidism was associated with iron deficiency and microcytosis. Anemia worsened during 1-year follow-up in nontreated patients, while L-thyroxine therapy promoted the normalization of hematological parameters, which was particularly evident in young and nonobese participants. A prospective clinical trial by Ravanbod et al[37] demonstrated that in the case of subclinical thyroid dysfunction accompanied by iron deficiency, the combination of L-thyroxine and iron salt was superior to each treatment alone. Thus, in order to achieve normalization of the hemoglobin and thyroid hormone status in the therapy of patients with subclinical hypothyroidism and iron deficiency, the method of choice is a simultaneous administration of L-thyroxine and iron preparation.[37] However, Shakir et al[38] reported that patients with anemia and hypothyroidism might not tolerate L-thyroxine therapy very well, because they may experience tachycardia, anxiety, and restlessness. Therefore, it seems reasonable that iron-deficient anemia should be corrected first, and L-thyroxine therapy should be postponed for a few weeks until hemoglobin level improves. Such a regimen might result in better tolerance of the therapy. Importantly, iron consumption might interfere with L-thyroxine absorption; therefore, it is better if these drugs are administered a few hours apart.[39] Sometimes, iron-deficient anemia might be the first symptom leading to the diagnosis of hypothyroidism, being the so called hematological mask of hypothyroidism.[40] Therefore, an unsuccessful therapy with oral iron preparations and recurrent sideropenia may require further evaluation of the underlying cause, which may be thyroid dysfunction.[41]

Pregnancy Both anemia and thyroid autoimmunity are frequently found in pregnant women. In fact, a decreased hemoglobin level observed during pregnancy develops predominantly due to hemodilution. In addition, a negative iron balance, caused by increased iron demand and preferential iron flow to the fetus irrespective of the mother's hemoglobin status, may lead to iron-deficiency anemia.[42]

In iodine-sufficient countries, AITD is the leading cause of thyroid dysfunction. According to recent research, autoimmunity features are present in 5% to 20% of pregnant women. Although anemia and thyroid dysfunction often coexist in pregnant women, the effect of the thyroid and metabolic state has only occasionally been the subject of research. In a study on pregnant women during the first trimester, thyroid function and antithyroid autoantibodies were significantly associated with the iron status. In women with iron deficiency, the incidence of AITD and subclinical hypothyroidism was significantly higher than in women without iron deficiency (20% vs 16% and 10% vs 6%, respectively). A significant negative correlation between ferritin and TSH levels was also observed, while free thyroxine levels positively correlated with ferritin levels. A logistic regression model demonstrated that iron deficiency was associated with AITD, even after correction for confounding factors, while the association with subclinical hypothyroidism was present only in a linear regression model.[43]

Gur et al[44] studied the incidence of anemia in pregnant women with AITD and subclinical hypothyroidism, euthyroid women with AITD, and

healthy pregnant women. They reported a significant positive correlation between hemoglobin and free thyroid hormone levels, and a negative correlation between hemoglobin and TSH levels. Hemoglobin levels were significantly lower in both groups with AITD regardless of thyroid function, compared with healthy controls. In addition, the authors found a significant positive correlation between hemoglobin and free thyroid hormone levels, along with a significant negative correlation between hemoglobin and TSH levels.[44] The results suggested that women with AITD are at higher risk of developing anemia during pregnancy, independent of the thyroid status. Therefore, women with previously known AITD should be more thoroughly screened for the occurrence of anemia during pregnancy, while profound anemia suggests the need to check the thyroid status of pregnant women if it was previously unknown. As both conditions might have a negative impact on pregnancy outcome, the simultaneous correction of both iron and thyroid hormone deficiency might positively influence the mother and child well-being.

Vitamin B_{12} deficiency, atrophic gastritis, and pernicious anemia leading to macrocytic anemia The most frequent cause of macrocytosis due to vitamin B_{12} deficiency is Addison–Biermer disease, or the so called pernicious anemia.[45] This autoimmune disease leads to the atrophy of gastric parietal cells, resulting in the lack of intrinsic factor and impaired hydrochloric acid secretion. This, in turn, leads to vitamin B_{12} malabsorption and anemia.[46] In these patients, antigastric parietal cell and anti-intrinsic factor antibodies may be detected.[47] In a study by Gerenova et al,[48] autoantibodies against parietal cells were positive in one-third of patients with AITD.

Centani et al[49] reported atrophic gastritis in 35% of patients with AITD, with the occurrence of pernicious anemia in 16% of the patients. A similar prevalence of atrophic gastritis in patients with AITD (40%) was revealed by Lahner et al.[50] Perros et al[51] reported that 6.3% of patients with type 1 diabetes and AITD were diagnosed with pernicious anemia. The risk was particularly increased in women, reaching 8.5%.[51] It is known that a large proportion of patients with pernicious anemia have increased antithyroid antibody titers; therefore, these patients are at risk of developing AITD. In a report by Chan et al,[52] 44% of patients with pernicious anemia showed evidence of antithyroid autoimmunity, which was more often diagnosed in women.

Of note, pernicious anemia in the course of HT may occur at any age. Anemia might be one of the clinical manifestations of congenital hypothyroidism in children and should imply further assessment of thyroid function.[53] Acquired hypothyroidism in the course of AITD was described in a 22-month-old child, whose symptoms also included macrocytic anemia and pallor, while L-thyroxine therapy allowed for the normalization of all clinical and biochemical parameters.[54]

Pernicious anemia frequently coexists with HT, but it might also belong to a spectrum of autoimmune disorders in the course of autoimmune polyglandular syndrome, or other diseases of partially autoimmune origin, such as myasthenia gravis.[55] Graves disease was also reported among the diseases observed in Schmidt syndrome (the most common form of autoimmune polyglandular syndrome, encompassing autoimmune adrenal insufficiency and AITD), together with pernicious anemia.[56]

Patients with AITD are at higher risk of developing vitamin B_{12}-deficiency anemia. However, Lippi et al[57] reported a significant correlation between TSH and folate concentrations, but not vitamin B_{12} concentrations. Symptoms of vitamin B_{12} deficiency may be poorly expressed and attributed to the underlying thyroid disease, or age. If such neuropsychiatric symptoms as weakness, motor disturbances, lethargy, memory loss, numbness, and tingling continue despite adequate L-thyroxine replacement, then the vitamin B_{12} concentration should be measured.[58] Jabbar et al[59] noted that numbness, paresthesia, and dysphagia were reported most often by hypothyroid patients with vitamin B_{12} deficiency, compared with those without the deficiency. Wang et al[60] noted that among patients with antithyroid antibodies attending an oral mucosal disease clinic, the most commonly reported symptoms were burning sensation of the tongue, dry mouth, lingual varicosity, and numbness of the tongue. The prevalence of vitamin B_{12} deficiency in hypothyroidism and AITD varies between studies and may depend on the ethnicity, eating habits, and nutritional status of the studied population (TABLE 1).[59]

Wang et al[60] found that 16.3% of patients with positive antithyroid antibody titers presented with anemia, 14.2% were iron-deficient, and 1.1% had folate deficiency. These rates were significantly higher than in healthy controls. Importantly, 85.8% of patients with AITD were clinically and biochemically euthyroid. Therefore, AITD might contribute to anemia by its mere presence and not only via the mechanism of developing hypothyroidism.[60] Conversely, in a study by Caplan et al,[61] serum folate and vitamin B_{12} levels in hypothyroid and euthyroid patients did not differ significantly. However, patients with pernicious anemia were excluded from the study.

When macrocytic anemia has a refractory course, and the therapy with vitamin B_{12} or folic acid does not bring expected hemoglobin level normalization, underlying hypothyroidism should be considered.[62] Such a combination suggests the possibility of autoimmune polyglandular syndrome. Therefore, personal or family history of hypothyroidism or pernicious anemia might be an important clue in the course of identifying occult pernicious anemia in the elderly.[63] Ness-Abramoff et al[64] recommended screening for vitamin B_{12}

TABLE 1 Prevalence of vitamin B_{12} deficiency in patients with hypothyroidism or autoimmune thyroid disease

Author	Threshold for vitamin B_{12} deficiency	Prevalence of vitamin B_{12} deficiency in the study group	Study group	Mean (SD) age of patients, y	Control group	*P* value[a]	Disease duration, y	Country
Jabbar et al[59]	<200 pg/ml	40.5%	116 patients with hypothyroidism (95 F, 21 M)	44 (13.7)	Not provided	Not provided	Not provided	Pakistan
Erdogan et al[15]	<189 pg/ml	25.6%	100 patients with subclinical hypothyroidism (85 F, 15 M)	44.9 (14.2)	200 healthy people	0.002	Not provided	Turkey
Erdogan et al[15]	<189 pg/ml	18.6%	100 patients with overt hypothyroidism (88 F, 12 M)	44.5 (13.9)	200 healthy people	0.002	Not provided	Turkey
Das et al[2]	Not provided	10%	60 patients (42 F, 18 M) with overt hypothyroidism (44) and subclinical hypothyroidism (16)	36.5	Not provided	Not provided	Not provided	Eastern India
Ness-Abramof et al[64]	≤133 pmol/l	28%	115 patients with AITD (108 F, 7 M)	47 (15)	Not provided	Not provided	Not provided	Israel
Jaya Kumari et al[58]	<200 pg/ml	55.5%	350 patients with AITD (250 F, 100 M)	32.2	Not provided	Not provided	2.4	South India
Wang et al[60]	<200 pg/ml	6.3%	190 patients with positive antithyroid autoantibodies (173 F, 17 M)	60.5 (11.7)	190 healthy people (173 F, 17 M; mean [SD] age, 60.5 [11.7] y)	0.139	Not provided	Taiwan

a significant difference between the study and control groups

Abbreviations: AITD, autoimmune thyroid disease; F, female; M, male

deficiency after initial diagnosis of AITD, and then repeat the screening periodically every 3 to 5 years, independently of the thyroid status. Pernicious anemia is currently listed as a risk factor for thyroid dysfunction; therefore, TSH screening in such patients is recommended.[65] However, conflicting literature data do not allow us to clearly assess the cost-effectiveness of such a management. Nevertheless, some authors suggest routine screening for AITD in patients with pernicious anemia.[66]

Hypothyroidism was the most prevalent cause of increased MCV assessed in the population with macrocytosis without anemia.[67] In patients with macrocytic anemia studied by Takahashi et al,[68] the most frequent cause was bone marrow abnormalities, although hypothyroidism was also one of the important contributing factors. Thus, thyroid dysfunction should be considered in a differential diagnosis of macrocytosis. However, when macrocytic anemia occurs in the course of hypothyroidism, MCV rarely exceeds 114 fl.[68]

Celiac disease One of the mechanisms contributing to anemia in patients with AITD are concomitant malabsorption syndromes, the most frequent of which is celiac disease. Celiac disease, especially the nonclassic type, might be unrecognized until adulthood. According to Farahid et al,[69] the incidence of histopathologically confirmed celiac disease is 5.7%, while the risk factors are older age (>40 years), presence of other autoimmune diseases, vitamin B_{12} deficiency, and anemia.

Symptoms of nonclassic celiac disease might be nonspecific, and often concern organs other than the gastrointestinal system. One of these might be refractory iron-deficiency anemia, symptomatic or detected incidentally during routine assessment of a patient with suspicion of AITD. The incidence of celiac disease is higher in patients with AITD than in the healthy population, and might affect even 8.6% of patients with HT. In a study on the Dutch population, 15% of patients with AITD had positive serology for celiac disease.[70] On the other hand, in total, 21% of celiac patients presented signs of AITD, of which 5% were euthyroid, 4% were subclinically hypothyroid, and 12% were diagnosed with overt hypothyroidism.[70] Therefore, in patients with AITD presenting with anemia, screening for celiac disease should be considered.

Autoimmune hemolytic anemia and Evans syndrome A rare cause of anemia in the course of AITD is Evans syndrome. The diseases may appear simultaneously, or may follow each other. In the pathogenesis of Evans syndrome, an autoimmune attack directed towards red blood cells and platelets plays a major role. As a result, patients present with autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura. To date, a few cases of HT and Evans syndrome have been described.[71] Comorbidity of Graves disease and Evans syndrome is also rare, and to the best of

our knowledge, so far 4 cases have been described in the literature.[72] Both Evans syndrome and AITD may share common immunological background. Insufficient suppressor T-cell activity and anti-TSH receptor autoantibodies, such as oligoclonal immunoglobulin G2 antibodies, are listed as potential pathogenetic factors.[73] Furthermore, Yasuda et al[74] suggested that autoimmune hemolytic anemia might be an effect of the stimulation of the activated reticuloendothelial phagocytic system by thyroid hormones. Recently, a case of Evans syndrome in the course of secondary hyperthyroidism caused by pituitary TSH--secreting adenoma has been described. Therefore, it was suggested that hyperthyroidism promoted autoimmunity itself, regardless of etiology.[74]

Symptoms such as severe fatigue developing in a patient with HT despite adequate L-thyroxine replacement therapy might indicate hemolytic anemia. Idiopathic thrombocytopenic purpura might occur simultaneously, but also following the first episode of autoimmune hemolytic anemia. In a patient described by Kang et al,[75] the time period was 2 years and the patient was finally diagnosed with Evans syndrome. Antithyroid autoantibodies are frequently observed in patients with Evans syndrome, which might suggest a common pathogenesis of these entities. Oh et al[76] reported a patient who had been suffering from HT for 13 years when autoimmune hemolytic anemia and primary immune thrombocytopenia developed. Hemolytic anemia might occur in the course of HT also in an isolated form, not accompanied by thrombocytopenia.[77] It is worth noting that autoimmune hemolytic anemia might be also a part of a spectrum of autoimmune disorders, including HT or autoimmune thrombocytopenia, in the course of Hodgkin lymphoma.[78] Although autoimmune hemolytic anemia in the course of AITD was only described in case reports, a possibility of Evans syndrome should be considered when a simultaneous presence of anemia and thrombocytopenia is detected in a patient with AITD.

Soft tissue rheumatic disorders Anemia in a patient with AITD might be related to the simultaneous occurrence of another autoimmune disease such as a soft tissue rheumatic disorder. A large cross-sectional study by Boelaert et al[79] showed that the most common autoimmune disease accompanying AITD was rheumatoid arthritis, which affected 3.15% of patients with Graves disease and 4.24% of patients with HT. Relative risks of almost all other studied autoimmune diseases in Graves disease or HT were significantly increased (>10 for pernicious anemia, systemic lupus erythematosus [SLE], Addison disease, celiac disease, and vitiligo). Many of these conditions might contribute to the development of anemia, which might be the first symptom of a rheumatic disease.[79] Anemia, mostly the normocytic type and of complex origin, may accompany many rheumatic disorders, including rheumatoid arthritis, SLE, or juvenile arthritis. In a study by Aikawa et al,[80] antithyroid autoantibodies were detected in 24% of patients with juvenile SLE. There were a few reports on patients with severe anemia due to pure red cell aplasia in the course of SLE, in whom accompanying diseases included hypothyroidism.[81] The prevalence of elevated antithyroglobulin antibody levels was found to be very high also in children population with juvenile chronic arthritis or SLE, and reached 63% and 58%, respectively.[82] This highlights the importance of screening for other autoimmune diseases if patients with AITD present with new or nonspecific symptoms such as anemia, increased body temperature, and small joint pain, which cannot be entirely attributed to the thyroid disease but may suggest a concomitant rheumatoid disorder.[83]

Chronic kidney disease Thyroid dysfunction, even subclinical, might importantly contribute to the development of anemia in patients with chronic kidney disease.[84] The analysis of patients on dialysis revealed that thyroid dysfunction occurs significantly more often in patients in whom the hemoglobin concentration is lower than 12.5 mg/dl. The most common type of thyroid abnormality is low T_3 syndrome defined as an abnormally low T_3 concentration, usually accompanied by normal TSH and free thyroxine concentrations, but not associated with primary thyroid disease. It is thought to be a mechanism of adaptation to a severe illness, namely, chronic kidney failure.

In patients with advanced renal function impairment, the production of erythropoietin is limited. Hence, in patients presenting more severe anemia, low T_3 syndrome occurs more often.[85] Both subclinical and clinical hypothyroidism constitute a risk factor for the development of chronic kidney disease within 5 years in patients above 65 years of age. Both these conditions may have an additive deteriorating effect on hemoglobin levels and increase the risk of anemia.[86] Su et al[87] found that the response to therapy with erythropoiesis-stimulating agents is not satisfactory in patients with subclinical hypothyroidism who are on dialysis due to chronic kidney disease. The dose of erythropoietin that needs to be used to treat anemia in such patients is significantly higher compared with that in euthyroid patients with renal function impairment, and the response to therapy improves following L-thyroxine administration.[88] Therefore, assessment of thyroid function seems mandatory in patients with chronic kidney disease and concomitant anemia resistant to therapy with erythropoiesis-stimulating agents.

Aplastic anemia Acquired aplastic anemia is a rare and life-threatening condition, characterized by hypocellular bone marrow and pancytopenia. Although in about half of the cases the cause is unknown, autoimmune response and exposure to certain drugs, chemicals, or radiation

are mentioned among the etiological factors.[89] Of note is that aplastic anemia may accompany other autoimmune disorders and may develop in the course of AITD. In fact, bone marrow aplasia is one of the very rare causes of anemia in the course of HT, and it was described mostly in case reports. Blaser et al[90] reported a case of a 62-year-old female patient presenting with HT complicated by eosinophilic fasciitis and aplastic anemia. A case of isolated red cell bone marrow aplasia in a patient previously diagnosed with HT was also reported.[91]

In patients with hyperthyroidism, aplastic anemia may occur in a iatrogenic form, as a side effect of antithyroid drug therapy. However, it occurs far less frequently than agranulocytosis, and affects approximately 0.1% to 0.5% of patients undergoing therapy for hyperthyroidism.[92] Nevertheless, the exact incidence of thiamazole-induced aplastic anemia remains unknown. Recently, a case of a child suffering from symptoms of severe aplastic anemia in the course of AITD has been reported.[93] Aplastic anemia is caused by T-lymphocyte hyperactivation which induces apoptosis of hematopoietic cells by the excessive secretion of Th1 lymphokines, such as interleukin 2 and interferon γ. Autoimmune disturbances in the course of Graves disease are the result of failure of T-suppressor cells to limit the expression of T-helper cells, sensitized to the TSH antigen, which interact with B cells. These cells differentiate into plasma cells which secrete anti-TSH receptor antibody. Therefore, both aplastic anemia and Graves disease seem to be caused by altered T-cell function.[93] Thus, AITD itself, as well as applied therapy with antithyroid drugs, may increase the risk of aplastic anemia. Although aplastic anemia is a rare finding in patients with thyroid dysfunction, it should be considered in a differential diagnosis of severe hematological disturbances, especially in a patient with autoimmune hyperthyroidism treated with thiamazole.

Conclusions Anemia in patients with thyroid diseases is a frequent, but often unrecognized, concomitant condition. Thyroid dysfunction and AITD should be considered in a differential diagnosis of anemia, especially of unknown origin. In patients with increased RDW, but without iron deficiency, thyroid function should be evaluated together with vitamin B_{12} and folate assessment. Thyroid dysfunction should also be considered if a treatment-resistant, or refractory, anemia occurs. Furthermore, attention must be paid to the hematological status of patients with thyroid disorders. The differential diagnosis of the etiology of anemia should include thyroid dysfunction, apart from the most common causes including iron, vitamin B_{12}, or folate deficiency, chronic kidney disease, and inflammatory disease. Additionally, vitamin B_{12} deficiency in the course of pernicious anemia may accompany thyroid dysfunction. Thus, in the case of vitamin B_{12} deficiency, TSH levels should also be measured. The presence of AITD, independently from thyroid hormone status, might affect the hemoglobin level. Some authors recommend screening for vitamin B_{12} deficiency on initial diagnosis of AITD, and periodically thereafter. However, there is not enough evidence to recommend regular screening for patients with hypothyroidism of nonautoimmune origin.

REFERENCES

1 M'Rabet-Bensalah K, Aubert CE, Coslovsky M, et al. Thyroid dysfunction and anaemia in a large population-based study. Clin Endocrinol (Oxf). 2016; 84: 627-631.

2 Das C, Sahana PK, Sengupta N, et al. Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India. Indian J Endocrinol Metab. 2012; 16: S361-S363.

3 Schindhelm RK, ten Boekel E, Heima NE, et al. Thyroid hormones and erythrocyte indices in a cohort of euthyroid older subjects. Eur J Intern Med. 2013; 24: 241-244.

4 den Elzen WP, de Craen AJ, Mooijaart SP, Gussekloo J. Low thyroid function and anemia in old age: the Leiden 85-plus study. J Am Geriatr Soc. 2015; 63: 407-409.

5 Refaat B. Prevalence and characteristics of anemia associated with thyroid disorders in non-pregnant Saudi women during the childbearing age: A cross-sectional study. Biomed J. 2015; 38: 307-316.

6 Vitale G, Fatti LM, Prolo S, et al. Screening for hypothyroidism in older hospitalized patients with anemia: a new insight into an old disease. J Am Geriatr Soc. 2010; 58: 1825-1827.

7 Konduracka E, Gajos G. Clinical characteristics of elderly patients with heart failure: what else do we need to know? Pol Arch Med Wewn. 2016; 126: 463-464.

8 Taylor S, Rampton D. Treatment of iron deficiency anemia: practical considerations. Pol Arch Med Wewn. 2015; 125: 452-460.

9 Omar S, Hadj Taeib S, Kanoun F, et al. [Erythrocyte abnormalities in thyroid dysfunction]. Tunis Med. 2010; 88: 783-788. French.

10 Lippi G, Montagnana M, Salvagno GL, Guidi GC. Should women with abnormal serum thyroid stimulating hormone undergo screening for anemia? Arch Pathol Lab Med. 2008; 132: 321-322.

11 Gianoukakis AG, Leigh MJ, Richards P, et al. Characterization of the anaemia associated with Graves' disease. Clin Endocrinol (Oxf). 2009; 70: 781-787.

12 Wilson GR, Curry RW Jr. Subclinical thyroid disease. Am Fam Physician. 2005; 72: 1517-1524.

13 Nekrasova TA, Strongin LG, Ledentsova OV. [Hematological disturbances in subclinical hypothyroidism and their dynamics during substitution therapy]. Klin Med (Mosk). 2013; 91: 29-33. Russian.

14 Bashir H, Bhat MH, Farooq R, et al. Comparison of hematological parameters in untreated and treated subclinical hypothyroidism and primary hypothyroidism patients. Med J Islam Repub Iran. 2012; 26: 172-178.

15 Erdogan M, Kosenli A, Ganidagli S, Kulaksizoglu M. Characteristics of anemia in subclinical and overt hypothyroid patients. Endocr J. 2012; 59: 213-220.

16 Christ-Crain M, Meier C, Huber P, et al. Effect of restoration of euthyroidism on peripheral blood cells and erythropoietin in women with subclinical hypothyroidism. Hormones (Athens). 2003; 2: 237-242.

17 Bremner AP, Feddema P, Joske DJ, et al. Significant association between thyroid hormones and erythrocyte indices in euthyroid subjects. Clin Endocrinol (Oxf). 2012; 76: 304-311.

18 Golde DW, Bersch N, Chopra IJ, Cline MJ. Thyroid hormones stimulate erythropoiesis in vitro. Br J Haematol. 1977; 37: 173-177.

19 Fandrey J, Pagel H, Frede S, Wolff M, Jelkmann W. Thyroid hormones enhance hypoxia-induced erythropoietin production in vitro. Exp Hematol. 1994; 22: 272-277.

20 Malgor LA, Blanc CC, Klainer E, et al. Direct effects of thyroid hormones on bone marrow erythroid cells of rats. Blood. 1975; 45: 671-679.

21 Dorgalaleh A, Mahmoodi M, Varmaghani B, et al. Effect of thyroid dysfunctions on blood cell count and red blood cell indice. Iran J Ped Hematol Oncol. 2013; 3: 73-77.

22 Malgor LA, Valsecia ME, Verges EG, de Markowsky EE. Enhancement of erythroid colony growth by triiodothyronine in cell cultures from bone marrow of normal and anemic rats with chronic renal failure. Acta Physiol Pharmacol Ther Latinoam. 1995; 45: 79-86.

23 Das KC, Mukherjee M, Sarkar TK, et al. Erythropoiesis and erythropoietin in hypo- and hyperthyroidism. J Clin Endocrinol Metab. 1975; 40: 211-220.

24 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.

25 Asl SZ, Brojeni NK, Ghasemi A, et al. Alterations in osmotic fragility of the red blood cells in hypo- and hyperthyroid patients. J Endocrinol Invest. 2009; 32: 28-32.

26 Khatiwada S, Gelal B, Baral N, Lamsal M. Association between iron status and thyroid function in Nepalese children. Thyroid Res. 2016; 9: 2.

27 Duntas LH, Papanastasiou L, Mantzou E, Koutras DA. Incidence of sideropenia and effects of iron repletion treatment in women with subclinical hypothyroidism. Exp Clin Endocrinol Diabetes. 1999; 107: 356-360.

28 Zimmermann MB, Kohrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid. 2002; 12: 867-878.

29 Potaczek DP, Jankowska EA, Wypasek E, Undas A. Iron deficiency: a novel risk factor of recurrence in patients after unprovoked venous thromboembolism. Pol Arch Med Wewn. 2016; 126: 159-165.

30 Sukumar SP, Balachandran K, Jayakumar, et al. Congenital hypothyroidism: an usual suspect at an unusual age: A case series. Indian J Endocrinol Metab. 2013; 17: S184-187.

31 Moragianni VA, Somkuti SG. Profound hypothyroidism-induced acute menorrhagia resulting in life-threatening anemia. Obstet Gynecol. 2007; 110: 515-517.

32 Blum M, Blum G. The possible relationship between menorrhagia and occult hypothyroidism in IUD-wearing women. Adv Contracept. 1992; 8: 313-317.

33 Aktas G, Sit M, Dikbas O, et al. Could red cell distribution width be a marker in Hashimoto's thyroiditis? Exp Clin Endocrinol Diabetes. 2014; 122: 572-574.

34 Montagnana M, Lippi G, Targher G, et al. C The red blood cell distribution width is associated with serum levels of thyroid stimulating hormone in the general population. Int J Lab Hematol. 2009; 31: 581-582.

35 Lippi G, Danese E, Montagnana M. Thyroid hormone levels are associated with anisocytosis in a cohort of euthyroid older outpatients. Eur J Intern Med. 2014; 25: e4-5.

36 Jafarzadeh A, Poorgholami M, Izadi N, et al. Immunological and hematological changes in patients with hyperthyroidism or hypothyroidism. Clin Invest Med. 2010; 33: E271-279.

37 Ravanbod M, Asadipooya K, Kalantarhormozi M, et al. Treatment of iron-deficiency anemia in patients with subclinical hypothyroidism. Am J Med. 2013; 126: 420-424.

38 Shakir KM, Turton D, Aprill BS, et al. Anemia: a cause of intolerance to thyroxine sodium. Mayo Clin Proc. 2000; 75: 189-192.

39 Campbell NR, Hasinoff BB, Stalts H, et al. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. Ann Intern Med. 1992; 117: 1010-1013.

40 Vydyborets SV. [Iron-deficiency anemia as a hematological mask of myxedema]. Lik Sprava. 1999; 148-150. Ukrainian.

41 Cinemre H, Bilir C, Gokosmanoglu F, Bahcebasi T. Hematologic effects of levothyroxine in iron-deficient subclinical hypothyroid patients: a randomized, double-blind, controlled study. J Clin Endocrinol Metab. 2009; 94: 151-156.

42 Bentley DP. Iron metabolism and anaemia in pregnancy. Clin Haematol. 1985; 14: 613-628.

43 Veltri F, Decaillet S, Kleynen P, et al. Prevalence of thyroid autoimmunity and dysfunction in women with iron deficiency during early pregnancy: is it altered? Eur J Endocrinol. 2016; 175: 191-199.

44 Gur EB, Karadeniz M, Inceefe H, et al. Thyroid antibodies in euthyroid and subclinical hypothyroidic pregnant women with autoimmune hypothyroidism: effects on hematological parameters and postpartum hemorrhage. Ginekol Pol. 2005; 86: 666-671.

45 Lacka K, Maciejewski A, Florczak-Wyspianska J [Coexistence of Addison-Biermer's disease with autoimmune thyroiditis – case report]. Pol Merkur Lekarski. 2013; 34: 40-44. Polish.

46 Collins AB, Pawlak R. Prevalence of vitamin B-12 deficiency among patients with thyroid dysfunction. Asia Pac J Clin Nutr. 2016; 25: 221-226.

47 Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: clinical picture and radiological findings. Nutrients. 2013; 5: 4521-4539.

48 Gerenova JB, Manolova IM, Tzoneva VI. Clinical significance of autoantibodies to parietal cells in patients with autoimmune thyroid diseases. Folia Med (Plovdiv). 2013; 55: 26-32.

49 Centanni M, Marignani M, Gargano L, et al. Atrophic body gastritis in patients with autoimmune thyroid disease: an underdiagnosed association. Arch Intern Med. 1999; 159: 1726-1730.

50 Lahner E, Centanni M, Agnello G, et al. Occurrence and risk factors for autoimmune thyroid disease in patients with atrophic body gastritis. Am J Med. 2008; 121: 136-141.

51 Perros P, Singh RK, Ludlam CA, Frier BM. Prevalence of pernicious anaemia in patients with Type 1 diabetes mellitus and autoimmune thyroid disease. Diabet Med. 2000; 17: 749-751.

52 Chan JC, Liu HS, Kho BC, et al. Pattern of thyroid autoimmunity in Chinese patients with pernicious anemia. Am J Med Sci. 2009; 337: 432-437.

53 Ghaemi N, Bagheri S, Elmi S, et al. Delayed diagnosis of hypothyroidism in children: report of 3 cases. Iran Red Crescent Med J. 2015; 17: e20306.

54 Marzuillo P, Grandone A, Perrotta S, et al. Very early onset of autoimmune thyroiditis in a toddler with severe hypothyroidism presentation: a case report. Ital J Pediatr. 2016; 42: 61.

55 Kuliszkiewicz-Janus M, Bednarek-Tupikowska G, Rozycka B, Deren I. [Coexistence of Addison-Biermer's anaemia with endocrine glands' dysfunctions]. Pol Arch Med Wewn. 2004; 112: 1311-1319. Polish.

56 Dasari S, Naha K, Hande M, Vivek G. Hot and cold: coexistent Graves' disease and Hashimoto's thyroiditis in a patient with Schmidt's syndrome. BMJ Case Rep. 2014.

57 Lippi G, Montagnana M, Targher G, et al. Prevalence of folic Acid and vitamin B12 deficiencies in patients with thyroid disorders. Am J Med Sci. 2008; 336: 50-52.

58 Jaya Kumari S, Bantwal G, et al. Evaluation of serum vitamin B12 levels and its correlation with anti-thyroperoxidase antibody in patients with autoimmune thyroid disorders. Indian J Clin Biochem. 2015; 30: 217-220.

59 Jabbar A, Yawar A, Waseem S, et al. Vitamin B12 deficiency common in primary hypothyroidism. J Pak Med Assoc. 2008; 58: 258-261.

60 Wang YP, Lin HP, Chen HM, et al. Hemoglobin, iron, and vitamin B12 deficiencies and high blood homocysteine levels in patients with anti-thyroid autoantibodies. J Formos Med Assoc. 2014; 113: 155-160.

61 Caplan RH, Davis K, Bengston B, Smith MJ. Serum folate and vitamin B12 levels in hypothyroid and hyperthyroid patients. Arch Intern Med. 1975; 135: 701-704.

62 Sims EG. Hypothyroidism causing macrocytic anemia unresponsive to B12 and folate. J Natl Med Assoc. 1983; 75: 429-431.

63 Catania J, Chaudhuri MD, Sitlani PK, Mannakkara JV. Hypothesis: a history of hypothyroidism or a family history of pernicious anaemia are useful in identifying masked pernicious anaemia in elderly patients with microcytic hypochromic anaemia. Age Ageing. 1989; 18: 279-281.

64 Ness-Abramof R, Nabriski DA, Braverman LE, et al. Prevalence and evaluation of B12 deficiency in patients with autoimmune thyroid disease. Am J Med Sci. 2006; 332: 119-122.

65 Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med. 2000; 160: 1573-1575.

66 Ottesen M, Feldt-Rasmussen U, Andersen J, et al. Thyroid function and autoimmunity in pernicious anemia before and during cyanocobalamin treatment. J Endocrinol Invest. 1995; 18: 91-97.

67 Dominguez Ruiz de Leon P, Morcillo Cebolla V, Gutierrez Parres B, et al. [Macrocytosis without anaemia in an urban population]. Aten Primaria. 2011; 43: 183-189. Spanish.

68 Takahashi S, Conti M, Van Wyk JJ. Thyrotropin potentiation of insulin-like growth factor-I dependent deoxribonucleic acid synthesis in FRTL-5 cells: mediation by an autocrine amplification factor(s). Endocrinology. 1990; 126: 736-745.

69 Farahid OH, Khawaja N, Shennak MM, et al. Prevalence of coeliac disease among adult patients with autoimmune hypothyroidism in Jordan. East Mediterr Health J. 2014; 20: 51-55.

70 Hadithi M, de Boer H, Meijer JW, et al. Coeliac disease in Dutch patients with Hashimoto's thyroiditis and vice versa. World J Gastroenterol. 2007; 13: 1715-1722.

71 Koti K, Thumma RR, Nagarajan S, Mathi A. Hashimoto's thyroiditis associated Evans syndrome: A rare case report on the clustered autoimmune disease triad. Indian J Endocrinol Metab. 2013; 17: 736-739.

72 Ushiki T, Masuko M, Nikkuni K, et al. Successful remission of Evans syndrome associated with Graves' disease by using propylthiouracil monotherapy. Intern Med. 2011; 50: 621-625.

73 Yashiro M, Nagoshi H, Kasuga Y, et al. Evans' syndrome associated with Graves' disease. Intern Med. 1996; 35: 987-990.

74 Yasuda A, Seki T, Oki M, et al. A case of a TSH-secreting pituitary adenoma associated with Evans' syndrome. Tokai J Exp Clin Med. 2015; 40: 44-50.

75 Kang MY, Hahm JR, Jung TS, et al. A 20-year-old woman with Hashimoto's thyroiditis and Evans' syndrome. Yonsei Med J. 2006; 47: 432-436.

76 Oh HJ, Yun MJ, Lee ST, et al. Evans syndrome following long-standing Hashimoto's thyroiditis and successful treatment with rituximab. Korean J Hematol. 2011; 46: 279-282.

77 Wasastjerna C. Two auto-immune diseases in one patient: a case of hemolytic anemia and Hashimoto's thyroiditis. Acta Med Scand. 1959; 165: 299-304.

78 Saitoh T, Matsushima T, Saito Y, et al. Hodgkin lymphoma presenting with various immunologic abnormalities, including autoimmune hepatitis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, and immune thrombocytopenia. Clin Lymphoma Myeloma. 2008; 8: 62-64.

79 Gogoi M, Sen AK, Baruah SM. Clinical study of anemia in rheumatoid arthritis. J Assoc Physicians India. 2016; 64: 151.

80 Aikawa NE, Jesus AA, Liphaus BL, et al. Organ-specific autoantibodies and autoimmune diseases in juvenile systemic lupus erythematosus and juvenile dermatomyositis patients. Clin Exp Rheumatol. 2012; 30: 126-131.

81 Fallahi S, Akbarian M, Dabiri S. Pure red cell aplasia as a presenting feature in systemic lupus erythematosus and association with thymoma,

hypothyroidism and hypoparathyroidism: a case report and literature review. Iran J Allergy Asthma Immunol. 2014; 13: 138-143.

82 Mihailova D, Grigorova R, Vassileva B, et al. Autoimmune thyroid disorders in juvenile chronic arthritis and systemic lupus erythematosus. Adv Exp Med Biol. 1999; 455: 55-60.

83 Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. Am J Med. 2010; 123: 183.e1-e9.

84 Bargenda A, Musial K, Zwolinska D. Subclinical hypothyroidism as a rare cofactor in chronic kidney disease (CKD) - related anemia. J Pediatr Endocrinol Metab. 2015; 28: 785-788.

85 Jusufovic S, Hodzic E, Halilcevic A. Role of renal anemia in the functional, morphological and autoimmune thyroid disorders in patients on chronic hemodialysis. Med Arh. 2011; 65: 228-232.

86 Chuang MH, Liao KM, Hung YM, et al. Abnormal thyroid-stimulating hormone and chronic kidney disease in elderly adults in Taipei city. J Am Geriatr Soc. 2016; 64: 1267-1273.

87 Su SC, Wu CC, Chen CC. Erythropoiesis-stimulating agent hyporesponsiveness in dialysis patients: be aware of subclinical hypothyroidism. Nephrology (Carlton). 2013; 18: 478.

88 Ng YY, Lin HD, Wu SC, et al. Impact of thyroid dysfunction on erythropoietin dosage in hemodialysis patients. Thyroid. 2013; 23: 552-561.

89 Peinemann F, Bartel C, Grouven U. First-line allogeneic hematopoietic stem cell transplantation of HLA-matched sibling donors compared with first-line ciclosporin and/or antithymocyte or antilymphocyte globulin for acquired severe aplastic anemia. Cochrane Database Syst Rev. 2013; CD006407.

90 Blaser KU, Steiger U, Wursch A, Speck B. [Eosinophilic fasciitis with aplastic anemia and Hashimoto's thyroiditis. Review of the literature and report of a typical example]. Schweiz Med Wochenschr. 1989; 119: 1899-1906. German.

91 Aranda C, Perez M, Herreros B, Penalver FJ. [Pure red cell aplasia and Hashimoto's thyroiditis: a rare association]. Med Clin (Barc). 2011; 137: 476-477. Spanish.

92 Thomas D, Moisidis A, Tsiakalos A, et al. Antithyroid drug-induced aplastic anemia. Thyroid. 2008; 18: 1043-1048.

93 Zhang W, Shao Z. Grave's disease following aplastic anemia: predisposition or coincidence? Indian Pediatr. 2015; 52: 347-348.