

Isolated non-autoimmune neutropenia revealing primary hypothyroidism

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Abstract

Introduction: hematological disorders are among the so-called unusual manifestations of hypothyroidism, and by far dominated by anemia. Leucocytes abnormalities are less common and often of an autoimmune nature. We report an original case of isolated non-autoimmune neutropenia revealing primary severe hypothyroidism.

Case report: A 30-year-old woman was referred by her family doctor for exploration of leucopenia at 3200/mm³. Control of the blood count confirmed isolated neutropenia at 600/mm³. The other parameters of the total blood count were without abnormalities: hemoglobin at 13g/dl, platelets at 162000/mm³, and lymphocytes at 2400/mm³.

Clinical examination, baseline bioassays, abdominal ultrasonography, thoraco-abdominopelvic CT, and myelogram were without abnormalities. Anti-nuclear, anti-native DNA, anti-nucleosome, and anti-neutrophil antibodies were negative.

Subsequent investigations concluded to primary hypothyroidism of Hashimoto's thyroiditis: TSH at 182μU/ml, FT4<1 pmol/l, anti-thyroglobulin antibodies at 255 IU/ml, and anti- thyroperoxidase antibodies at 1000 IU/ml. The patient was treated with thyroxine in progressive doses until normalization of TSH with 175μg/d. The evolution was favorable with neutrophils at 2200/mm³ after one month of treatment.

Conclusion: Isolated and non-autoimmune neutropenia indicative of hypothyroidism is exceptional and unusual representing a real diagnostic challenge for clinicians. It is recommended to screen for thyroid dysfunction in front of any leucopenia that does not prove itself.

Introduction

Hypothyroidism is one of the most common endocrinopathies in the world with an estimated prevalence of 0.3-3.7% for overt or symptomatic forms [1] and more than 10% for subclinical or asymptomatic forms [2]. This prevalence can be as high as 20% in subjects over 60 years of age, especially women [3,4], and it is estimated that 2.5% of subjects with subclinical form progress to overt hypothyroidism annually [5].

Despite their frequency and ease of diagnosis, these endocrinopathies remain underdiagnosed; in fact, a meta-analysis of studies in nine European countries estimated the prevalence of undiagnosed cases of hypothyroidism (both overt and subclinical) at 5% of the general population [6]. The large polymorphism of clinical and biological manifestations associated with hypothyroidism explains the under-diagnosis of this disease [7-11].

Hematological disorders are among the so-called unusual manifestations of hypothyroidism [12]. They are therefore very little known and often overlooked by health practitioners [12]. Hematological manifestations of hypothyroidism are by far dominated by anemia [12,13] and pancytopenia [14,15]. Leucopenia/neutropenia are much rarer and unusual [16] and are classically autoimmune in nature (autoimmune neutropenia associated with autoimmune thyroiditis) [17,18]. We report the original case of isolated and non-autoimmune neutropenia revealing primary severe hypothyroidism.

Case report

A 30-year-old woman with no significant pathological history was referred by her family doctor for exploration of isolated leucopenia at 3200/mm³, found on a systematic check-up. Control of the blood count confirmed isolated leukopenia of neutropenia-type with neutrophils at 600/mm³. The other parameters of the total blood count were without abnormalities: hemoglobin at 13g/dl, platelets at 162000/mm³, and lymphocytes at 2400/mm³.

The clinical examination was without particularities. Baseline bioassays were within normal limits: erythrocyte sedimentation rate, C-reactive protein, serum calcium, inogram, lactic-dehydrogenases, alkaline phosphatase, serum protein electrophoresis, blood glucose, transaminases, muscle enzymes, lipid parameters, and creatinine. Anti-nuclear, anti-native DNA, anti-nucleosome, and anti-neutrophil antibodies were negative.

Abdominal ultrasonography and thoracoabdominopelvic CT were without abnormalities. The myelogram with marrow karyotype

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was also without abnormalities. Subsequent investigations concluded to primary hypothyroidism of Hashimoto's thyroiditis: Thyroid Stimulating Hormone (TSH) at 182 μ U/ml, free tetraiodothyronine (FT4) <1 pmol/l, anti-thyroglobulin antibodies at 255 IU/ml, and anti-thyroperoxidase antibodies strongly positive at 1000 IU/ml.

The final diagnosis was that of a severe subclinical hypothyroidism of Hashimoto's thyroiditis, revealed by isolated non-autoimmune neutropenia. The patient was treated with thyroxine in progressive doses until normalization of TSH with 175 μ g/d. The evolution was favorable with progressive normalization of the leucocyte count. Neutrophils were at 2200/mm³ after one month of treatment.

Discussion

Hematological manifestations during hypothyroidism are dominated by anemia [12,13] with a wide variety of anemic disorders (normocytic, microcytic, and macrocytic) [13], and sometimes even severe pancytopenia [14,15]. More rarely are platelet function abnormalities, and coagulation factor alterations [19]. Leucocytes abnormalities are much rarer and unusual during hypothyroidism [16] but can sometimes be severe with even cases of agranulocytosis [20].

The exact frequency of leuco-neutropenia during hypothyroidism is not well known due to lack of studies. In an Algerian study presented at the 34th Congress of the French Society of Endocrinology in 2017, Haddam AEM et al reported a frequency of 6% of leucopenia in their series of 150 untreated hypothyroid patients [21]. The following year, and at the 35th congress of the same society, the Tunisian team of Guizani N et al reported a frequency of 4% of leucopenia in their series of 67 hypothyroid patients [22]. This frequency seems to be very underestimated since in the Kyritsi EM et al study of 218 patients investigated for neutropenia, 95 had a thyroid disorder (43.6%) and half had hypothyroidism [18]. This same study showed that the prevalence of hypothyroidism in neutropenic patients is statistically higher than that in the general population: 23.4% Vs 10.7-13.4% [18].

Neutropenia associated with hypothyroidism can be exceptionally isolated as in our case, but most often associated with other hematological disorders (anemia, macrocytosis, lymphopenia, and thrombocytopenia) [16,23,24]. It is classically mild to moderate but can exceptionally be severe [20].

The exact physiopathological mechanism of this neutropenia is not well understood. It may be a direct repercussion of thyroid hormone deficiency on the various stages of hematopoiesis [25], in particular granulopoiesis [18], or an autoimmune mechanism (autoimmune neutropenia with positive anti-neutrophil antibodies) during hypothyroidism of autoimmune thyroiditis [17,18].

These hematological disorders may be the dominant signs of the clinical picture of this endocrinopathy or, exceptionally, the only signs revealing or inaugurating the disease [12,24]. Hematological disorders, including leucopenia/neutropenia, typically respond favorably to hormone replacement therapy for hypothyroidism [12]. Failure to correct these hematological abnormalities with hormone replacement therapy should be suggestive of underlying hematologic malignancies (acute myeloid leukemia or myelodysplastic syndrome) [23].

Conclusion

Isolated leucopenia/neutropenia indicative of hypothyroidism is very rare and unusual representing a real diagnostic challenge for clinicians. Non-autoimmune forms related to a direct effect of thyroid hormone deficiency are exceptional and respond favorably to

treatment with thyroxine. Their knowledge by all health practitioners is necessary to avoid diagnostic delays and costly and often unnecessary investigations. Thus, hypothyroidism should be considered in the differential diagnosis of neutropenia and it is recommended to screen for thyroid dysfunction in front of any leukopenia that does not prove itself.

Conflict of interest

None

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