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The role of surgery in polyautoimmunity: Graves Disease associated with Autoimmune Pernicious Anemia or pancytopenia

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Abstract

Introduction: Polyautoimmunity is defined as the presence of more than one autoimmune disease in a single patient. Among these syndroms Graves' disease represents the endocryne prototype of such disorders. However the coexistence of hyperthyroidism with autoimmune or nonautoimmune conditions is rarely described.
Patients reports: 138 patients with hyperthyroidism were hospitalized over more than four decades for surgical treatment. 53 cases had medical hisory of salient Graves' disease, either untreated or refractory to treatment. Hematologic indices, thyroid functions and inflammatory parameters were examined at presentation and following successful thyroidectomy. Two patients, both female, 43 and respectively 45 years old, receiving long standing treatment with antithyroid drugs(propylthiouracil) and beta blockers(propranolol) obtaining unsubstantial clinical improvement with stationary or even increased size of the diffuse goiter presented also with persistent megaloblastic anemia and respectively pancytopenia, thus raising the suspicion of their assignment to the endocrine disease. Additional studies identified the real nature of the hematologic abnormalities and ruled out other causes of anemia or cytopenia. Diagnostic was also confirmed by pathology reports and postoperative remission of hematological alterations

Keywords: Graves' Disease, Pernicious Anemia, Autoimmune Disorders, Surgical Treatment

Introduction.

Endocrine immunological disorders, with various anatomical-clinical background often present different concomitant or sequential comorbidities. Such is the case of thyroid pathology associated with one or more several autoimmune diseases [1,2]. The incidental association between hyperthyroidism of Graves' disease, the prototype of these autoimmune disorders and pernicious anemia or respectively pancytopenia, both of them being also established autoimmune disorders, is infrequent. Even if these joint conditions are rarely recognized they should be always considered in the differential diagnosis of hematologic disorders to prevent wrong diagnosis, useless investigations and therapeutic medical or/and surgical gestures. They remain sporadically mentioned in literature but their pathogenic mechanism involved is still insufficiently understood [3-6].

Patients and method: In our series of 138 cases of different clinical forms of hyperthyroidism operated on in a four decades period among which 53 observations of Graves' disease (GD) only two patients have presented this rare association, both of them after prolonged standing treatment with conventional antithyroid drugs and β-blockers, obtaining unconvincing clinical improvements but stationary or even increasing size of their diffuse goiters. To these illustrative cases we also add two observations of common "simple" GD anemia which corrected promptly with return to the euthyroid state following thyrotoxicosis appearing as a epiphenomen of disease and one case of Iron defficiency anemia due to celiac disease where it was not clear that surgery influenced the course.

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Cases reports:

One each case of GD associated with autoimmune pernicious anemia (APA) and respectively autoimmune pancytopenia (AIP) were diagnosed and treated appropriately in our clinic. Both our patients with GD related with anemia received adequate and treatment with antithyroid drugs (propylthiouracyl) and β-blockers (propranolol) obtaining notable clinical improvement despite their stationary or even increased size of diffuse goiters but also persistence of associated chronic anemic syndrome. Finally persistence of thyroid enlargement but also obstinacy of some of clinical and biological complaints determined the patient to decide and request surgical solution.

First case reports a underweight 43-years-old female under treatment with methimazol from one year for typical GD. Irregular or often interrupted medical therapy led to a capricious evolution of symptoms but even an increase in her goiter volume . She also accused remittent palpitations, anxiety and irritability, nervousness, heat intolerance and wet skin, irregular menstrual periods fine tremors of the hands together with progressive weight loss of about 8 kg in this period. Clinical and US examination showed an enlarged diffuse thyroid gland measuring about 9x6 cm (Fig 1,2) without nodules, thrill or bruit associating minimal lid lag but without pretibial mixedema or acropachy. Clinically, chest examination was nomal and the heart rhythm was regular with a rate of 100/min with systolic murmur over the cardiac base but no click or gallop. Blood pressure was 130/70 mmHg. She was pale with hiperhidrosis. Lymphadenopathies were absent. The abdomen was soft and non-tender with liver edge palpable 2 cm below right costal margin and spleen not palpable.However, the presence of paleness of the skin, fatigue, shorteness and dizzeness evoke the rare possibility of an associate anemic syndrome. A complete blood count however confirm the diagnosis of pernicious anemia: hemoglobin was 7,8 mg/dl, WBC count 3400/µL platelet count 98000/µl, reticulocyte count 25,9%, bilirubin 4.0 mg/dl, LDH 320 U/l, positive. Failure of treatment due to irregular or even interupted medical therapy leading to whimsy evolution of symptomatologyy and even an increase in goiter volume and refusal of radioiodine use determined our proposal for surgery and a near total thyroidectomy was practiced whitout dificulties or incidents.

Fig 1. Clinical aspect of our 43-years-old patient

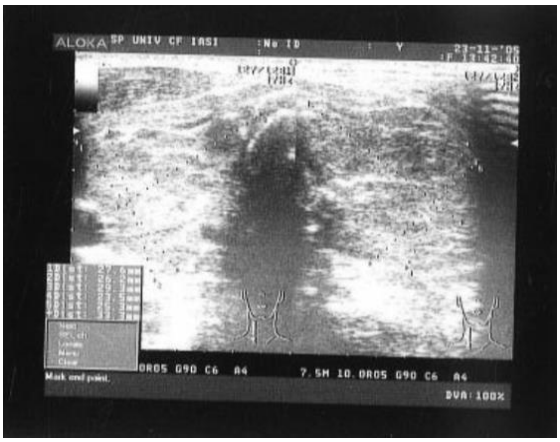

Fig 2. Preoperative ultrasonography of our patient

Fig 3. Same patient: operative specimen

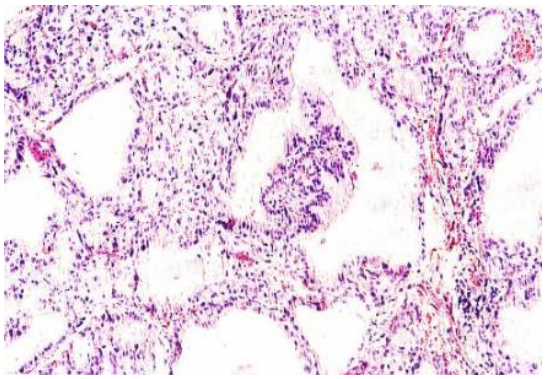

Fig 4. Same patient: histopathological appearance

Operative specimen counting 120 g objectived the ordinary irregular hyperplasia and evidencied all histologic features of thyroid hyperfunction.(Fig 3,4) Immediate and postoperative periodic controls showed the vanishing or regression of most symptoms including also the hematologic abnormalities. Our patient retured to a stable existence aided by minimal medical corrections achieving euthyroidism by use of levothyroxine. Its hematological component was handled using prednison and rituxibam. Even if in most situations administration of antithyroid drugs or 131 I are considered the main preffered actual therapies of GD and its systemic complications, in this particular case only the surgical solution was however applicable. Also for blood components of this disorder, corticosteroids in adaptated doses and periods combined with immunosuppressive medication conducted by hematologist offered favorable results.

Second case report exhibits also a less known hematologic disease associated with GD, this time with pancytopenia , reffering to decreases in all peripheral blood lineages and considered to be present when all three cells lines are below to the normal reference range within the overall framework of a such a case. Our case reports a 40 year-old woman with a long standing less salient GD treated from two years with antithyroid drugs (propylthiouracil) and β-blockers (propranolol) recording a notable clinical improvement but with stationary or even increase size of her diffuse goiter (Fig 5). She presented also moderate lid lag but not ophtalmopathy, and a regular hearth rhithm with a rate of 100/bpm and a blood pression of 140/80 mmHG, palled wet skin, giddiness, tiredness, anorexia and coldness of the extremitities, acropachy, pretibial mixedema (Fig 6). Current thyroid scan and US revealed a difuse 8x5 cm homogeneous, hypervascularised thyroid (Fig 7). Laboratory workup showed TSH=3,6 mU/L, fT4=38 pmol/L, fT3=9 pmol/L, TRAB 1,8 UI/L. Thorough full blood count indicated pancytopenia with normochromic, normocytic anemia Ht=32%, Hb=9g/dL, MCV=88 fL, MHCH=34 q/L. Also total white count was 3400 u/L, platelet count was 48000 u/L and reticulocyte count was 1%. Peripheral blood smears shows oval macrocytes, hypersegmented granulocytes so a diagnosis of megaloblastic anemia secondary to Vitamin B12 deficiency was established. The standard treatment with intramuscular cyanocobalamin obtained substantial resolution of woman's symptomatology. However maintaned thyroidomegaly prompted our patient to undergo surgery. An adjusted near total thyroidectomy (Dunhill's tehnique) was practiced followed by a smooth postoperative course.

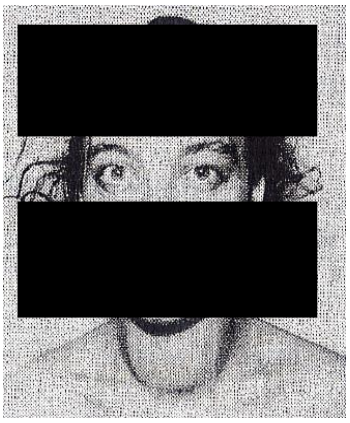

Fig 5. A 40-old-year female with GD and anemia

Fig 6. Pretibial mixedema of our patient

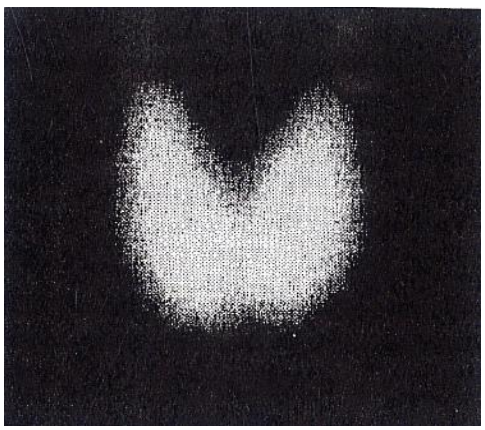

Fig 7. Graves' disease: thyroid scintigraphy

Fig 8. Same case. Operative specimen

The operative specimen weighed 150 g (Fig 8) and histological examination showed all stigmas of thyroid hyperfunction. Astonishing endocrine equilibration was obtaining together with positive hematological response occuring gradually within few months and maintaining further. Both these two cases can be included in group of polyimmunopathic syndromes with concomitant or successive onset , evolution or cessation. The two patients presented, although associating anemic syndromes with a pretty common glandular status-thyrotoxicosis, have promptly shown corrected hematoligical indices after surgical treatment, with return to the normal clinical and hormonal equilibrium.

Discussions.

Autoimmunity is defined the pathological process in which the body's immune system assaults its own cells and tissues, a process in which genetics plays a central role in combination with external factors such as environmental life style and even past infections [7,8]. In 1993 Sheehan and Stanton propose their own concept of polyautoimmunity syndromes defined by presence of more than one autoimmune disease in a single patient, as well as effect of a single genotype on diverse autoimmune phenotypes. [9]

General opinion is that etiopathogenesis of these immunological associations does not include a single mechanism of humoral and/or cellular immune response, more probable being the possibility of normal immune response regulation impairement based on a particular genetic predisposition [10]. Between many conditions determined by this mechanism, endocrine diseases as thyroid hypo- and hyper-function belong to the group of autoimmune disorders taking a heriditary component which is associated with numerous other organ or systemic autoimmune conditions. Among them are included hematopoietic troubles such as the different forms of anemia constituting genuine autoimmune poly-glandular syndromes [11]. This pathology gathers a heterogeneous group of rare diseases characterized by autonomous activity directed against at least more than one endocrine gland, although an non-endocrine organ can also be affected.

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice [12]. An estimated one-third of world's population lives in areas of low dietary iodine levels. In regions of severe iodine deficiency the prevalence of goiter is as high as 80%. Graves' disease which is an autonomous endocrine condition accounts for up to 60-80% of hyperthyroidism cases and is estimated to affect 0.5% of the population [13, 14,15]. Beyond the common classical signs and symptoms of main thyroid diseases a significant number of distinct associated features were described, some constituting in true syndromes whose autoimmune origin enhance the above mentioned concept of polyautoimmunity. Of course the diagnosis and treatment of these all related disorders is up hampered with corresponding results and prognosis.

The association between GD with different clinical forms of anemias or other systemic hematologic conditions constitutes the subject of more and more publications about their real frequency, causes, clinical and diagnostic elements but also therapy and especially connections between those disorders which remains ambiguos from their initial disclosures [14,15].

In the same time, different forms of anemia correspond 24,8% of the general population and were usually found in 33% of patients with thyroid hyper function, being some challenging to face it as the presenting feature of GD, especially when the typical events are subtle or prospective. In this atypical association with GD, anemia appears in different forms: pernicious anemia, hemolytic anemia, iron deficiency anemia in celiac disease, or simple normochromic normocyticanemia (this last variety being fugitive, appearing with GD and disappearing concomitantly with its cure 6,14].

Autoimmune Pernicious Anemia (APA) first described by J Combe, T Addison and A Biemer in the 19th century is a well-known rare form of autoimmune disease that may occur in association with GD with a prevalence of 0,15-1,4% in general population [17,18,19]. APA is an autoimmune disorder in which there is an immune response against the Gastric H/K-ATPase causing Vit B12 deficiency [20]. This leads to a decrease in the synthesis of the intrinsic factor produced by parietal cells in the gastric mucosa. However the exact pathogenesis of GD anemia still remains indistinct, though an effect of excess thy-roid hormones has been postulated. Ford and Carter also suggested that hematological changes associated with GD might relate to the underlying immunologic disturbance in the endocrine disorder [6]. The finding of megaloblastic anemia (marked macrocytosis with hypersegmented polymorphonuclear leucocytes) in the peripheral blood of a GD subject should raise the suspicion of this association [12]. Otherwise the chronic and frequently insidious evolution of both sufferings are difficult to explain their concomitant or successive appearance, realized also - excepting pathognomonic events (mainly in GD) of each entity – several confusions looking common clinical manifestations such as agitation, nervousness, weakness, sweating, tingling, numbness, motor disturbances, palpitations, tachycardia, shortness of breath, weight loss, pale skin and so on. All this requires in all cases a thorough and repeated clinical, laboratory and imaging exploration completed by a eventually sample therapy [18,19]. Although APA is frequently founded in medical practice but its common appearance together with different anatomical-clinical varieties of thyroid diseases is much less signaled. However various authors underline that only pernicious anemia and pancytopenia who have similar autoimmune pathogenic component coexists with thyroid conditions (GD, Hashimoto thyroiditis). The first disorder is the most frequent cause of hyperthyroidism and results from production of autoantibodies that bind to surface of erythrocytes and stimulate the TSH receptors suggesting the autoimmune basis of GD anemia. [16]. Further evolution and complications of GD occur by two main actions: the first is the ensuing thyreotoxic condition which can affect almost every organ system in the body

and the second is the concurrent autoimmune process and association with other autoimmune diseases [19,20].

Treatment of GD associated with APA included consistent measures against both conditions, such as administration of synthetic antithyroid drugs, radioactive iodine or surgery, each of them with own indications, benefits and risks and the treatment choice is made in accordance to the age, patient preference, presence of other co-morbidities, individual characteristics of the cases and availability of certain treatment modality [21, 2]. GD therapy is effective on the majority of complaints, also influencing numerous subjective and objective manifestations related to those of anemia [23 ,24]. The last disorder must be however be carefully monitored over time and treated for life with vitamin B12 preparations, maintaining constant the level of cobalamine in the individual former thyreotoxicosis patient. Finally the possibility of simultaneous or successive presence of autoimmune forms of hyperthyroidism and autoimmune pernicious anemia is rarely described [25,26].

Pancytopenia (PCP) coexisting with GD is pointed significantly more less marked than another adjoining autoimmune disorders being limited to a small number of case presentations. [27, 28].) The first writings about this rare pathologic tandem also signals the presence of other autoimmune diseases [29, 30]. PCP is a serious hematologic disorder that, apart from primary marrow failure it may be consecutive to several condition including infections, radiations, (cytotoxic) drugs and certain metabolic diseases [31]. Among the latters the association between GD and PCP is reported less commonly [32, 33].

Review of the literature showed that the majority of these cases are middle-aged women, pancytopenia preceding hyperthyroidism with some years, is usually chronic and well tolerated and in most of them hematologic values are corrected with treatment of the tryroid disease. In another cases thyrotoxicosis is manifested initially or both conditions occur at the same moment. The true pathogenesis of this association remains unclear but seems to be related to both hyperthyroidism and autoimmunity [34]. Causes of PCP even poorly understood suggest a double mechanism of anemia: reduced production of hematopoietic cells from the bone marrow and increased destruction or sequestration of mature hematopoietic cells. Indeed thyroid hormones are known for their effect on erythropoiesis, through hyperproliferation of immature erythroid progenitors and enhanced secretion of erythropoietin, producing different forms of anemia. Hyperhormonemia has notable effects on erythropoiesis though hyperproliferation of immature erythyroid progenitors and increased secretion of erythropoietin [35]

The occurance of leucopenia is also poorly understood. Decresed granulopoiesis due to reduced marrow granulocyte reserve and also the possibility of immunologic destruction mechanism are plausible. Thereby GD represents one of the most common disorder among patients with mild neutropenia. In addition antiplatelet antibodies have been detected in the serum of GD' patients [36, 37].

However the possibility of association of two or more well-defined autoimmune diseases suggesting the term of polyautoimmunity or autoimmune diathesis remains plausible. Between these at least one typical autoimmune endocrine autoimmune disease can be linked with another autoimmune lesion or systemic illness. Potential interest in management of cases of coexisting GD with PCP can be use of antithyroid medication (thioamides i.e propylthiouracyl, carbimazole), radioiodine ablation or even surgery and normalizing of thyrotoxicosis is followed by correction of the blood cell count. When surgical decision in case of GD was taken, pancitopenia's treatment continued in parallel with routine preoperative preparation. Postsurgical pursuit concern both in endocrinology and hematology plan. Postsurgical evolution required both endocrine and anemic syndrome surveillance, the latter much more difficult to control and treat in time. In spite of common pathogenic mechanisms the two entities retain probably distinct genetic elements that give them different evolutionary possibilities. [38,39, 40] . All studies including also our modest intervention established that autoimmunity encompasses a wide spectrum of diseases and epidemiological, pathogenesis and clinical coexistence between GD and hematological troubles as PA and pancytopenia or other related, must always be evoked upon onset of one of this disorders. Report of these less frequent conditions require further documentation and analysis.

Conclusions.

Most patients with GD usually present with manifestations of functional overactivity with and less often without classical presence of ocular signs and/or goiter. However thyroid hormone excesses influencing practically every organ or physiological system may sometimes affect atypically or predominantly these structures and some of them also significantly disturbing hematopoietic functions. So alterations of erythropoiesis, red cell mass, shortened erythrocyte survival and abnormal iron conscription and application, conduced of course in a larger autoimmune context, to more associate syndromes among which different forms of anemia. Several autoimmune antibodies were found but a common autoimmune mechanism was not clearly showed. Genetic factors may play also an important role in the pathogenesis of association from GD and these diverse forms of anemia. Studies establishing that autoimmunity encompasses a wide spectrum of diseases and epidemiological, pathogenic and clinical coexistence between GD and systemic troubles as autoimmune pernicious anemia and pancytopenia and must always evoked when we are confronted with one of these disorders. Reports of both such less frequent presentations obliged to further documentation and analysis of eventual reciprocal influence. Treatment of this rare pathologic tandem can resort to antithyroid drugs, radioiodine or rarely surgery. All cases requires life-long surveillance and eventual prompt correction of any abnormal evolution occurred.

Outside the main classical clinical presentation, these condition can also be depicted through the lack of some of them, predominance of atypical or less important manifestation or establishment of some non-specific signs and symptoms of coexistent autoimmune or even no autoimmune disorders all of these delaying, confusing or even obstructing adequate therapy.

Conflict of Interest

Authors have no conflict of interest to disclose

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