# Autoimmune thrombocytopenia

## *Is it a different disease or different aspects of a single disease?*

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## ABSTRACT

**الأهداف**: دراسة العلاقة بين نقص الصفائح الدموية والأمراض المناعية الذاتية الأخرى وذلك من أجل إثبات ما إذا كانت هذه الأمراض مختلفة أو مرض واحد مع العديد من المظاهر التي ترافقه في نفس الوقت، بالإضافة إلى دراسة تأثير العلاج على عدد الصفائح الدموية مع اختلاف حالة الغدة الدرقية.

**الطريقة**: أُجريت هذه الدراسة الاسترجاعية في قسم الدم، مستشفى الملك عبدالعزيز الجامعي، جدة، المملكة العربية السعودية خلال الفترة من يونيو 2003م إلى أغسطس 2010م. شملت الدراسة 141 مريض مصاب بنقص الصفائح الدموية. ولقد قمنا بتحليل وظيفية الغدة الدرقية، والأجسام المضادة الذاتية للغدة الدرقية، وتفاعل كوومبز، والأجسام المضادة للنواة، وشريط الحامض النووي المزدوج.

**النتائج**: لقد وُجد أن 51 مريض (36.2%) من المرضى يعانون من علامات أمراض المناعة الذاتية، و13 مريض (9.2%) يعانون من انخفاض نشاط الغدة الدرقية، و6 مرضى (4.3%) من زيادة نشاط الغدة الدرقية. ولقد وجد أيضاً أن 5 مرضى (3.5%) لديهم علامات مخبرية بالإصابة بمتلازمة إيفانز، بالإضافة إلى ظهور الأجسام المضادة للغدة الدرقية في 3 مرضى (2.1%). ولم يكن هناك فروق واضحة من الناحية الإحصائية في عدد الصائح الدموية بعد شهر واحد من العلاج وذلك مع اختلاف حالة الغدة الدرقية ($p$=0.61).

**خاتمة**: هناك أدلة على أن مرضى نقص الصفائح الدموية يعانون من خلل مناعي في أجهزة الجسم المختلفة مثل الغدة الدرقية أو حدوث مرض الذئبة الحمراء مما يتطلب متابعة المرضى بالتحاليل المخبرية لتشخيصها مبكراً.

**Objectives:** To evaluate the association between autoimmune thrombocytopenia with other autoimmune disorders, to show if they are different autoimmune diseases or one disease with different presentations at the same time, and to study the effect of treatment on platelet count in different thyroid condition.

**Methods:** In this retrospective study, we included 141 patients with thrombocytopenic purpura. The result of thyroid function test, thyroid autoantibodies, Coombs' reactivity, anti-nuclear antibody, and double-stranded DNA were analyzed. This study was conducted in the Clinical Hematology Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia between June 2003 and August 2010.

**Results:** There were 51 (36.2%) patients with laboratory evidence of autoimmune disease, 13 (9.2%) with hypothyroidism, and 6 (4.3%) with hyperthyroidism. In addition, 5 (3.5%) patients showed laboratory evidence of Evan syndrome and 3 (2.1%) patients had isolated positive thyroid antibodies. There was non-significant difference ($p$=0.61) in platelets count after one month of treatment of patients with different thyroid condition.

**Conclusion:** Immune thrombocytopenia is associated with evidence of different autoimmune disease or a combination of them, which may appear at presentation or during the course of disease giving evidence that they are different manifestations of a single disease. Screening patients for antithyroid antibodies would identify a patient at risk of developing overt thyroid disease. These patients may be further screened with a thyroid-stimulating hormone assay to detect subclinical thyroid disease.

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Autoimmune thrombocytopenic purpura (AITP) is a form of destructive thrombocytopenia which can be either idiopathic, also known as primary immune thrombocytopenic purpura (ITP), or secondary to other autoimmune disorders.[1] In AITP, one can often elicit systemic lupus erythematosis (SLE), Hashimoto's thyroiditis, rheumatoid arthritis, or other autoimmune disorder, but there is few literature about the incidence of these autoimmune antibodies or a combination between them. There are several case reports of Evans syndrome or SLE occurring simultaneously or following an autoimmune thyroid disease (AITD) as Graves's disease,[2,3] or Hashimoto's thyroiditis.[4] It was speculated that in thyroid diseases, thrombocytopenia might be secondary to an activation of the reticulo-endothelial phagocytic system by thyroid hormones or to a platelet immune destruction.[5-7] Associations exist between AITP, autoimmune thyroid diseases (AITD) and other autoimmune disorders but, the full extent of these associations is still not fully appreciated.[4,8] For a better understanding, the effect and estimation of the incidence of overlapping autoimmune markers in patients with AITP, we evaluated the association between AITP, AITD, markers of SLE, and Evan syndrome and examined the effect of treatment on platelet count in different thyroid condition. We are hoping to give evidence that primary ITP is best thought of as single disease with different presentation that could be present at diagnosis or during the course of treatment and the patients should be investigated for this at frequent intervals.

**Methods.** This study included retrospective analysis of clinical records of 141 patients with ITP followed up in the Clinical Hematology Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia between June 2003 and August 2010. We excluded the patients with thrombocytopenia if it was due to hypersplenism, drug induced or congenital causes. Fifty-one out of 141 ITP patients have laboratory finding of autoimmune disease as positive anti-nuclear antibody (ANA), double-stranded DNA (ds-DNA), direct antiglobulin test (DAT), thyroid autoantibodies as antithyroglobulin antibody (TgAb), and thyroperoxidase antibody (TPOAb). According to the result of thyroid function test (TFT) and clinical data, they are divided into 3 groups (32 patients with normal TFT, 6 patients with hyperthyroidism, and 13 patients with hypothyroidism).

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We considered the patient in euthyroid state if they had normal T3, T4, and thyroid-stimulating hormone (TSH); clinical hyperthyroidism if T3 and T4 was high and low TSH; and receiving antithyroid drugs or radioactive iodine. If the patient has low TSH level, but with normal T3 and T4, we defined it as subclinical hyperthyroidism. We defined clinical hypothyroidism if T3, T4 was low, but with high TSH and under treatment with thyroxin hormone. Subclinical hypothyroidism was defined if the patient had mild increased of serum TSH levels (4.5-10 mIU/liter) with normal T3 and T4. The patient was considered to have SLE based on positive ANA >1/80 with ds-DNA and low C3 and C4. We estimated the incidence of laboratory markers of autoimmune disease as ANA, ds-DNA, Coombs' reactivity, thyroid antibodies, and the effect of thyroid status on the response to treatment after one month. Data were assessed according to the normal reference ranges of laboratories as follows: TSH (0.27-4.2 IU/L), ANA (1:40), dS-DNA (0-200 IU/ml), TPOAb (0-34 IU/ml), and TgAb (0-115 IU/ml).

Data were analyzed using the Statistical Package for Social Sciences for windows, version 15 (SPSS Inc., Chicago, IL, USA). Differences were evaluated using student t-test. A *p*-value less that 0.05 was considered as statistically significant.

**Results.** **Tables 1 and 2** show that among 141 patients with immune thrombocytopenia, there were 90 (63.8%) patients with idiopathic thrombocytopenic purpura with negative laboratory tests for autoimmune disease during their follow up and 51 (36.2%) patients with autoimmune thrombocytopenia. There were 32 (22.7%) with normal TFT, 13 (9.2%) with hypothyroidism and 6 (4.3%) with hyperthyroidism. Based on the presence of autoimmune markers, there was high incidence of positive ANA + ds-DNA in 43 (30.5%) patients, Evan syndrome was recognized in 5 (3.5%) patients and 3 (2.1%) patients had isolated positive thyroid antibodies. The female to male ratio was 3.6:1 and there was no effect of thyroid status on the platelets count after one month of treatment ($p$=0.61) as presented in **Table 2**.

**Table 1** - Incidence of markers of autoimmune disease in patients with autoimmune thrombocytopenic purpura.

| Patients | n | (%) |
|---|---|---|
| Idiopathic (no cause) | 90 | (63.8) |
| Autoimmune thrombocytopenia | 51 | (36.2) |
| Total positive ANA, ds-DNA, DAT, or thyroid autoantibodies | 43 | (30.5) |
| Evan syndrome | 5 | (3.5) |
| Positive thyroid autoantibodies only | 3 | (2.1) |
| **Total** | **141** | **(100.0)** |

ANA - anti-nuclear antibody, ds-DNA - double-stranded DNA, DTA - direct antiglobulin test

**Table 2 -** Characteristics of 51 patients with autoimmune thrombocytopenic purpura and the effect of thyroid disease with outcome after one month of treatment with steroids.

| Patient's characteristics | Male n (%) | Female n (%) | Age (years) Mean±SD | Platelet at diagnosis | Platelet after treatment |
|---|---|---|---|---|---|
| Euthyroid (n=32) | 8 (15.7) | 24 (45.0) | 30.7 ± 17.6 | 14.7 ± 13.7 | 113 ± 130 |
| Hyperthyroidism (n=13) | 2 (3.9) | 11 (21.6) | 30.7 ± 16.3 | 12.5 ± 12.1 | 103 ± 75 |
| Hypothyroidism (n=6) | 0 (0.0) | 11 (11.8) | 16.5 ± 9.0 | 19.7 ± 24.4 | 150 ± 90 |
| Total (n=51) | 11 (21.6) | 40 (78.4) | 26.0 ± 8.20 | 15.6 ± 3.6 | 124 ± 24.8 |
| *P*-value | | | | 0.75 | 0.61 |

**Table 3 -** Clinical significance of autoantibodies in immune thrombocytopenia during follow up.

| Clinical significance | n | (%) |
|---|---|---|
| Thyroid diseases | 22 | (15.6) |
| Clinical hypothyroidism | 2 | (1.4) |
| Subclinical hypothyroidism | 4 | (2.8) |
| Clinical hyperthyroidism | 3 | (2.1) |
| Subclinical hyperthyroidism | 10 | (7.1) |
| Normal TFT with positive thyroid autoantibodies | 3 | (2.1) |
| Clinical and laboratory SLE (Positive ANA and ds-DNA ) | 7 | (5.0) |
| Significant antibodies | 29 | (20.6) |
| Non-significant antibodies | 112 | (79.4) |
| **Total** | **141** | **(100.0)** |

TFT - thyroid function test, SLE - systemic lupus erythematosus, ANA - anti-nuclear antibody, ds-DNA - double-stranded DNA, DTA - direct antiglobulin test

**Table 4 -** Incidence of different combination of markers of autoimmune disease in patients different thyroid status (N=51).

| Thyroid status | ANA ds-DNA (n=43) | Thyroid AB (n=10) | Coombs' reactivity (n=9) |
|---|---|---|---|
| ***Euthyroid (n=32)*** | | | |
| 27 (52.9%) | Positive | Negative | Negative |
| 1 (2%) | Positive | Positive | Negative |
| 2 (3.9%) | Negative | Negative | Positive |
| 1 (2%) | Negative | Positive | Positive |
| 1 (2%) | Negative | Positive | Negative |
| ***Hyperthyroidism (n=6)*** | | | |
| 2 (3.9%) | Positive | Positive | Negative |
| 4 (7.8%) | Positive | Negative | Positive |
| ***Hypothyroidism (n=13)*** | | | |
| 3 (5.9%) | Positive | Positive | Negative |
| 6 (11.8%) | Positive | Negative | Negative |
| 2 (3.9%) | Negative | Negative | Positive |
| 2 (3.9%) | Negative | Positive | Negative |

ANA - anti-nuclear antibody, ds-DNA - double-stranded DNA

**Table 3** shows the clinical significance of autoantibodies where 2/6 patients have clinical hypothyroidism, 3/13 have clinical hyperthyroidism, and 7/43 with positive ANA have SLE.

**Table 4** shows that there is no specific pattern of occurrence of autoantibodies and give evidence that there is overlapping trait in AITP where 1 patients in euthyroid state and 3 with hyperthyroidism had both ANA , ds-DNA with thyroid AB positive , 4 patients with hypothyroidism had positive ANA, ds-DNA with Coombs' reactivity, one patients in euthyroid state had both thyroid antibodies positive with Coombs' reactivity, and 2 with hyperthyroidism had Coombs' reactivity. There were 10 patients with positive thyroid antibodies where 3 have only thyroid antibodies and 6 patients have thyroid antibodies with positive ANA.

**Discussion.** The association between thrombocytopenia, with organ specific or non organ specific autoimmune disease as AITD or SLE has long been recognized,[8,9] but the cases are few and consequently questioning the possibility of association but could not prove that a true association exists.[10] In our study we found association between AITP, thyroid diseases and markers of autoimmune diseases as (ANA, ds-DNA, DAT, and thyroid antibodies in 36.2% of studied group. 21.6% of them had hyperthyroidism and 11.8% have hypothyroidism and this is similar to what is reported by Valenta et al[11] who showed that approximately 13% of patients with primary AITP may develop hyperthyroidism, also Richard Hyer[12] reported that, the estimated prevalence of hyperthyroidism in conjunction with immunologic thrombocytopenia was between 5% and 14%. and the estimated prevalence of hypothyroidism 5%. In our study there were 37 (30.4%) patients who had positive ANA + ds-DNA, which is similar to Pratt et al 2005(7) who reported that children with acute ITP, (23%) of them had an acute non platelet autoantibody and (33%) of the children with chronic ITP had at least one abnormal antibody value, 5 children (16%) tested positive for anti thyroid antibody (ATA) and had positive ANA. Our results also are in agreement with Liebman[10] who reported that 8-14% of ITP patients developed hyperthyroidism during follow up and others developed antibodies to thyroglobulin and may eventually develop hypo or hyperthyroidism. Also with Ioachimescu et al[13] who found 16/80 patients with AITP (20%) had abnormal thyroid function: 6 (7.5%) had hyperthyroidism and 10(12.5%) had hypothyroidism. In our study we found 2 patients with hypothyroidism and 6 with hyperthyroidism who had

positive ANA and ds-DNA which is similar to Kataura et al[14] who reported 14/16 patients with Graves disease and 7/32 with Hashimotos thyroiditis had positive anti ds-DNA, and this give evidence that some patients may start with single autoimmune disease and may progress to another disease.

In our study their was a good response after one month of treatment and the thyroid condition showed no effect on the platelets response to steroids and this in agreement with Ioachimescu et al 2007[13] who reported that treating thyroid disease in patients with immunologic thrombocytopenia will not correct platelets alone and treatment of the thyroid disease did not show any change in 13/16 patients and only 3 patients showed transient response, but this was against Takebayashi et al[2] who reported a case report of a 40-year-old woman with ITP and Graves disease and after treatment with an antithyroid agent (methimazole), both the Graves disease and thrombocytopenia resolved. Our data seems to rule out an effect of thyroid hormone on platelet count and it is apparent that AITD are part of autoimmune manifestation during the course of ITP. In our study most the patients presented as autoimmune thrombocytopenia and thyroid disease discovered during the course of treatment.

This study document an association between ITP, autoimmune thyroid diseases and other systemic autoimmune diseases. This could reflect a more progressive defect in the immune self-tolerance of these patients which may make those patients are more refractory to standard ITP therapy.

In conclusion, such findings confirm the existence of an overlap syndrome between ITP, SLE, and AITD and we suggest that primary ITP is best treated as ITP syndrome even with one autoimmune disease where the likelihood of having another autoimmune disease is greater during the course of the disease. We recommend screening for antithyroid antibodies would identify a patient population at greater risk of developing overt thyroid disease. These patients may be further screened with a TSH assay to detect subclinical thyroid disease.

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