Is Autoimmune Thrombocytopenia Itself the Primary Disease in the Presence of Second Diseases? Data from a Long-Term Observation

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Keywords

Autoimmune thrombocytopenia · Secondary autoimmune thrombocytopenia · Evans syndrome · Antibody deficiency syndrome · Platelets

Summary

Background: Dependent on the absence or presence of associated diseases, autoimmune thrombocytopenia (ITP) can be classified as primary or secondary form. The manifestation of the associated diseases is not temporally defined and may occur during observation. Thus the question which disease is the primary one remains unanswered. **Methods:** All 386 patients included in this study were treated by a single primary physician between 1996 and 2015 at the Charité Berlin and met current ITP criteria. Medical records and investigations were reviewed to assess diseases associated with ITP. **Results:** Initially, the vast majority of patients presented with primary ITP (isolated disease). Based on our findings, ITP was found to be associated with other abnormalities in most cases. These abnormalities included: positive direct antiglobulin test in 49 of 386 tested patients (13%), affections of the thyroid gland in 41 of 386 tested patients (11%), infections in 30 (8%), solid malignancies in 20 (5%) and hematological malignancies in 10 patients (3%), as well as many other miscellaneous diseases. Moreover, of 160 patients who did not receive prior intravenous immunoglobulin treatment, 40 (25%) showed antibody deficiency. **Conclusion:** In conclusion, the incidence of ‘true’ ITP as a primary disease is less common than has yet been suggested. Additionally, there is evidence that ITP itself predispose affected subjects toward development of other diseases.

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Introduction

Autoimmune thrombocytopenia (ITP) is one of the best characterized autoimmune diseases. Based on clinical and laboratory findings, it is classified into primary (idiopathic) and secondary forms. While the primary form is defined as an isolated disease, the secondary form is associated with at least one underlying disease/abnormality [1–5].

In general, it is accepted that approximately 80% of ITP patients suffer from the primary form and the remaining patients have a secondary form. The diseases associated with the secondary form include lupus erythematosus (5%), infections e.g., HCV, HIV, and *Helicobacter pylori* (6%), post-vaccination syndrome (1%), antiphospholipid syndrome (2%), lymphoma (2%) and Evans syndrome (2%) [6]. However, a systematic analysis of the incidence of secondary ITP is lacking [6]. Ultimately, data available thus far are largely based on the diagnosis at first presentation without systemic assessment of affected patients. In addition, it may take months or even years until the clinical manifestation of the associated disease becomes obvious, e.g., malignancies. Finally, the causative primary underlying disease/abnormality may remain unrecognized in asymptomatic patients, e.g., in those with clinically inconspicuous antibody deficiency. Thus, the incidences of ‘true’ primary or secondary ITP are not only speculative, but also arbitrary in many cases.

In this study, we re-examined the diagnoses in patients with chronic ITP (>1 year), since we observed that many patients had developed or had yet unrecognized relevant diseases and/or abnormalities which appeared to play a role in the pathogenesis of ITP. In addition, there is evidence that ITP itself might be a predisposing factor for the development of some other diseases.

Patients and Methods

All 386 patients in this study (132 male, 254 female; age: 3–101 years, mean: 51 years) met chronic ITP criteria [3]. The diagnosis of ITP was first made between 1959 and 2015 (mean 2005). All patients were treated on an outpatient basis by a single physician between 1996 and 2015 at the Institute of Transfusion Medicine of the Charité – Universitätsmedizin Berlin, Germany. All medical records and investigations were reviewed retrospectively to assess possible causes of ITP. Serum and platelets, if available in a sufficient amount during an active phase of the ITP, were investigated by the indirect and direct monoclonal antibody-specific immobilization of platelet antigen assay (MAIPA) as described by Meyer et al. [7]. Serological testing of red blood cells (RBCs) was performed in all patients using the standard gel technique. The presence of “true” RBC autoantibodies was confirmed by testing the eluate of patients’ RBCs [8]. The concentrations of IgG, IgA, and IgM were measured in 160 patients using rate nephelometry (Beckman Coulter, Krefeld, Germany) and ELISA (IMTEC Immundiagnostika, Berlin, Germany). Immunoglobulins were not measured in patients who had recently received intravenous immunoglobulin (IVIG) treatment. Similarly, free T₃ (triiodothyronine), T₄ (thyroxine), and TSH (thyroid-stimulating hormone) were tested in patients who were not under treatment with thyroid or antithyroid drugs. If indicated, additional parameters, e.g. antinuclear autoantibodies (ANA), rheumatoid factors (RF), anti-double stranded DNA and anti-viral hepatitis antibodies were also tested. This study was approved by the institutional ethic review board (EA2/058112). Informed consent was obtained from all patients.

Results

According to the criteria previously defined [1–5], at least 222 (58%) of the 386 patients included appeared to have a secondary rather than a primary ITP (table 1). The most common associated disorder was autoimmunization against RBCs, with 49 of 386 patients (13%) being tested positive by the direct anti-human globulin test (DAT). Other common associated diseases were antibody deficiency in 40 of 160 patients (25%), affection of the thyroid gland in 41 of 386 patients (11%), and infections in 30 of 386 patients (8%) (tables 1, 2). Other diseases and abnormalities included solid malignancies, hematological malignancies, psoriasis, rheumatoid arthritis, collagenoses (tables 1, 2), and other miscellaneous diseases (table 3). We considered a possible association between ITP and a second disease only if both diseases were present at the same time or the relationship between the diseases was well-known, e.g. solid malignancies or autoimmune diseases. Most importantly, the association with other diseases/abnormalities could not be made during the first investigation and/or only became obvious during further observation. In addition, the abnormalities as-

Table 1. Patients with significant and/or insignificant underlying disease/abnormality that may be causative for ITP or vice versa

Underlying disease/abnormality	Patients with one relevant underlying disease/abnormality (n)	Patients with one additional relevant underlying disease/abnormality (n)	Patients with two additional relevant underlying diseases/abnormalities (n)	Patients with three additional relevant underlying diseases/abnormalities (n)
Evans syndrome	22	6× AD, 4× TG, 4× COLL, 2× INF, 1× APS, 1× HPC, 1× PS	2× AD + TG, 1× drug-induced + INF, 1× MS + APS, 1× COLL + R.A., 1× HM + AD, 1× AD + PS	1× COLL + APS + TG
Antibody deficiency	19	4× TG, 2× INF, 1× COLL, 1× solid malignancy	1× MS + suspicion of drug-induced, 1× solid malignancy + suspicion of drug-induced	1× PS + R.A. + TG
Solid malignancy	14	1× suspicion of drug-induced, 1× PS, 1× INF, 1× TG		
Infection	15	4× HPC, 3× drug-induced, 1× HM, 1× TG		
Affection of the thyroid gland	25	1 × COLL	1 APS + COLL	
Rheumatoid arthritis	8	1× COLL	1× PBC + COLL, 1× MDS + INF	
Hematological malignancies	7	1× MDS		
Suspicion to be drug-induced	7		1× APS + COLL	
Psoriasis	6	1× HPC		
Collagenosis	4	1× Sneddon syndrome		
Miscellaneous diseases	33	2		
Total patients	160	47	13	2
AD = Antibody deficiency; APS = antiphospholipide syndrome; COLL = collagenosis; Evans = Evans syndrome; HM = hematological malignancies; HPC = hepatic cirrhosis; IBD = inflammatory bowel disease; INF = infection; MDS = myelodysplastic syndrome; MS = multiple sclerosis; PBC = primary biliary cirrhosis; PS = psoriasis; R.A. = rheumatoid arthritis; TG = affection of thyroid gland.				

Table 2. Character of diseases/abnormalities associated to ITP

	Patients (n)
<i>Antibody deficiency</i>	
IgG deficiency	29
IgG, IgM and IgA deficiency	4
IgA deficiency	3
IgM deficiency	1
IgG and IgA deficiency	1
Humoral dysregulation (IgG2 elevation, IgG4 deficiency and IgM elevation)	1
IgG and IgM deficiency	1
Total	40
<i>Affection of thyroid gland</i>	
Hypothyroidism	18
Hashimoto thyroiditis	14
Hyperthyroidism	7
Morbus Basedow	2
Total	41
<i>Solid malignancy</i>	
Breast cancer	6
Melanoma	4
Prostate cancer	2
Borderline ovarian adenocarcinoma	1
Ovarian cancer	1
Merkel-cell carcinoma	1
Colon cancer	1
Sigmoid cancer	1
Rectal cancer	1
Bladder cancer	1
Bronchial cancer	1
Total	20
<i>Infection</i>	
HCV	10
HBV	5
<i>Borrelia</i>	4
<i>H. pylori</i>	3
HIV	2
<i>Borrelia</i> and <i>H. pylori</i>	1
HCV + schistosomiasis	1
HIV and HCV	1
HBV and HCV	1
<i>Helicobacter</i> eradication (remission afterwards)	1
Tuberculosis	1
Total	30

sociated with the ITP were often asymptomatic and without clinical significance. Only 17 of 49 (35%) patients with detectable autoantibodies to RBCs had or developed significant hemolysis, and 4 of 40 (10%) patients with antibody deficiency had significant disposition to infection and required IgG substitutions. In contrast, the vast majority of patients with thyroid diseases required treatment with thyroid hormones.

Most intriguingly, there was no clear sequence regarding the occurrence of ITP and other diseases/abnormalities. In some cases,

Table 2. Continued

	Patients (n)
<i>Hematological malignancies</i>	
Chronic lymphocytic leukemia	2
Chronic myelogenous leukemia	2
Hodgkin's lymphoma	2
T-cell non-Hodgkin's lymphoma	1
Chronic myelomonocytic leukemia	1
B-cell non-Hodgkin's lymphoma	1
Suspicion of non-Hodgkin's lymphoma	1
Total	10
<i>Collagenosis</i>	
Lupus erythematosus	11
Undifferentiated collagenosis	3
Mixed collagenosis with Raynaud's syndrome	1
Sjögren's syndrome	1
Suspicion of lupus erythematosus (laboratory positive)	1
Total	17

ITP was the first manifestation, later followed by other diseases/abnormalities. In others, the reverse was true. For example, 4 of 6 patients with breast cancer were first diagnosed with ITP and only later to suffer from breast cancer, while the other 2 were first diagnosed with breast cancer and then developed ITP. Similarly, 4 of 10 patients with hematological malignancies developed ITP before the malignancy could be detected, whereas 6 were first diagnosed with hematological malignancies and later with ITP. Of 11 patients suffering from psoriasis, 7 were diagnosed with ITP at a later point while 4 received ITP as primary and psoriasis as secondary diagnosis. Similarly, 3 of 5 patients with multiple sclerosis developed ITP, and 2 patients with ITP developed multiple sclerosis during the observation period. In addition, we believe some other patients may have had asymptomatic multiple sclerosis. Eight of 11 patients appeared to have developed lupus erythematosus prior to the manifestation of ITP.

Finally, it cannot be predicted whether or not other patients with 'true' ITP will develop secondary diseases during further observation.

Discussion

In this study, we focused on the occurrence and/or presence of secondary diseases and abnormalities in patients with chronic ITP. At first glance, the majority of these patients appeared to have isolated ITP. Similar to other studies dealing with long-term outcomes of patients with chronic ITP, our observations show that many affected patients developed a second disease as a complication of ITP [9–13]. Together, these findings reflect different etiologic observations which should be considered in further studies.

Firstly, the current ITP classification into primary and secondary types is not reliable and in many cases inaccurate. At least 58% (n = 222) of our patients with ITP exhibited other abnormalities

Table 3. Character of miscellaneous diseases that may be causative for ITP or vice versa

Underlying diseases/abnormalities	Patients (n)
Drug-induced	5
MDS	4
PBC	3
IBD (1× Morbus Crohn; 2× colitis ulcerosa)	3
Anti-TPO	3
MS	3
APS	2
HPC	2
Thymom	2
Coomb's-negative hemolytic anemia	1
Polymyalgia rheumatica	1
Hip implant-induced	1
Pituitary adenoma	1
Sneddon's syndrome	1
Sneddon's syndrome + APS	1
Sarcoidosis	1
Elevated ANA + amalgam (remission after detoxification)	1
Total	35

Anti-TPO = Thyroid peroxidase antibody; APS = antiphospholipide syndrome; HPC = hepatic cirrhosis; IBD = inflammatory bowel disease; MDS = myelodysplastic syndrome; MS = multiple sclerosis; PBC = primary biliary cirrhosis.

with or without clinical manifestation, e.g., DAT positivity, antibody deficiency, malignancies, or other diseases and abnormalities (table 1).

Secondly, the prevailing concept in ITP diagnosis considers the associated disease as the primary one. This might be the case in many but not in all instances. In some cases, ITP itself might be responsible for the development of associated diseases. This is supported by the fact that the manifestation of ITP may sometimes occur a long time prior to the manifestation of the associated disease. However, a true association between ITP and other diseases cannot be proven invariably due to the long period of time between occurrence and manifestation and/or diagnosis of the diseases.

In case of Evans syndrome, both cytopenias may occur simultaneously, the ITP may precede the onset of the autoimmune hemolytic anemia (AIHA) or vice versa. In the latter case, the interval between the manifestations of both cytopenias varies between several months and several years [14]. In addition, autoimmune neutropenia may occur in association with AIHA and/or ITP. However, the true incidence of these associations remains obscure due to the fact that the majority of the affected patients require treatment, e.g. steroids, to prevent the manifestation of a second cytopenia. Ultimately and in agreement with the first description of Evans and Duane [15], the autoantibodies to RBCs do not invariably cause hemolysis, and the affected patients may only suffer from ITP and/or neutropenia. Similarly, malignancies are a product of a complicated process that may halt several years until the disease becomes evident. Thus, it is impossible to determine when the primary tumor first developed and when the onset of tumor-associated dysregulation occurred for the first time. Since platelets are also involved in the process of malignancies [16, 17], it remains

unclear which disease is the primary and which is the secondary one. Recently, we identified many differentially expressed oncoproteins and tumor suppressor proteins in ITP [18]. This finding supports the hypothesis of an interaction between platelets and many malignancies [16, 17].

The results of MAIPA were inconclusive since the direct test could not be performed in patients with very low platelet counts. In addition, the results were dependent on platelet count and the type of therapy the patients received. The autoantibodies may disappear or remain undetectable when platelet counts increase to $\geq 50 \times 10^9/l$ (e.g., following treatment with steroids), or they may remain detectable even when the ITP enters into complete remission (e.g., following splenectomy).

There is no doubt that platelets play a key role in the immune continuum, including the release of various chemokines, cytokines, and many other mediators. Platelets are known to directly interact or to mediate interaction with all or nearly all immune cells [19–22]. Moreover, we have recently identified a large number of differentially expressed proteins in ITP. In addition to oncoproteins and tumor suppressor proteins, several specific autoantibodies occurring in other autoimmune diseases were also detectable in ITP [18]. Thus, the supposition cannot be dismissed that ITP might be the primary disease stimulating the development of other diseases (including malignancies and other autoimmune diseases or phenomena). However, it cannot be excluded that the associated diseases frequently induce the development of ITP, even in cases where ITP occurs prior to the manifestation of the primary disease. Whatever the primary disease may be, there is ample evidence that a reciprocal influence exists between ITP and associated diseases. It is beyond the scope of this study to highlight the biology of plate-

lets in the immune continuum, but we must update our historic viewpoint on this subject. Platelets are not only essential to hemostasis but also actively participate in immunity. Meanwhile, more than 1,000 proteins, of which 69 are membrane proteins, have been shown to be associated with platelets, and a large number of these molecules play a role in immune processes [23, 24]. This is supported by a number of clinical findings such as the significant correlation of fatigue and 'pseudoarthritis' in ITP with low platelet counts [25–29].

In both cases, the affected patients frequently attribute their repeated suffering from tiredness and/or joint pains to having low platelet counts. These symptoms, however, cannot be explained by low platelet count alone but rather by an unrecognized interaction of platelets or their contents with other regulatory cells and cell receptors. Finally, serotonin has been shown to be involved in fatigue syndrome [30–33] and different forms of immune-mediated arthritis [34], and platelets are the main carriers for serotonin [35–37]. A previous study showed that neuropharmacological

treatment resulted in an increase of platelet counts in at least 5 patients suffering from ITP [38]. Moreover, platelets have been shown to be implicated in several autoimmune conditions, including lupus erythematosus, rheumatoid arthritis, sclerodermitis, and multiple sclerosis [19, 39–41].

We are aware of the limitations of the present study, which are mainly due to its retrospective character. In addition, the number of ITP patients with associated hematological malignancies is inadequately represented due to the fact that we did not treat patients primarily suffering from malignancies, e.g. lymphoma. Thus, new sophisticated studies are required to gain deeper insights into the interactions and causal relationships of ITP with other diseases.

Disclosure Statement

All authors declare that they have no conflict of interests due to sponsorship or funding arrangements related to this study.

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