Autoimmune thrombocytopenia in non-Hodgkin's lymphomas

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ABSTRACT

Autoimmune thrombocytopenia is a common immune-hematologic complication in non-Hodgkin's lymphomas and may complicate the treatment. We analyzed an original series from our institute as well as published cases of non-Hodgkin's lymphomas (excluding chronic lymphocytic leukemia) associated with autoimmune thrombocytopenia with regard to demographic factors, prevalence in non-Hodgkin's lymphoma subtypes and treatment outcome. The male/female ratio is 1.75. Half of the cases occurred prior to diagnosis of lymphoma. Chemotherapy is the best treatment in many non-Hodgkin's lymphomas patients with autoimmune thrombocytopenia compared with standard treatment of autoimmune thrombocytopenia. Splenectomy is effective in splenic marginal zone lymphoma. Autoimmune thrombocytopenia in patients with non-Hodgkin's lymphomas is potentially life-threatening and difficult to treat.

Key words: autoimmune thrombocytopenias, non-Hodgkin's lymphoma.

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Introduction

Autoimmune phenomena are associated with non-Hodgkin's lymphoma (NHL). They may precede the clinical presentation of NHL, occur concurrently or later, either spontaneously or following treatment.[1-3] Among these phenomena, hematologic autoimmune diseases are a special subgroup and include autoimmune hemolytic anemia (AIHA),[4] autoimmune thrombocytopenia (ITP), Evans's syndrome, antibodies to clotting factors,[5] lupus anticoagulants[6] and antibodies to C1 esterase inhibitor.[7] Less is known about the occurrence, prognosis and treatment of ITP in NHL. The frequency of ITP in chronic lymphocytic leukemia (CLL) and NHL has been determined in several studies[8-15]

We analyzed data of individual non-CLL NHL patients with ITP from published case reports and original series of our institute with regard to the temporal relationship between ITP and lymphoma, the frequency in NHL subtypes, laboratory data and treatment outcome.

Design and Methods

Data were taken from case reports published in the literature (n=32) with minimal diagnostic information on the underlying NHL (excluding B-CLL) and ITP as well as from an original series (one case of an associated ITP in 292 patients with lymphoma) from our institute. The case reports were retrieved using PubMed and Medline (1962-2006) and from the reference lists of papers published in the field. The histological diagnosis of the lymphomas was made according to NHL classification at the time of publication. We converted the lymphoma diagnosis of the authors to the WHO classification.[16] Treatment outcome was taken to be that confirmed by the authors: complete remission=CR; partial remission=PR; no remission or refractory=NR. The term transient complete remission=tCR was used in cases in which there was a relapse after initial successful treatment. Two authors independently analyzed data. Statistical methods were not applied due to the small number of cases.

Results

Overall prevalence of ITP in NHL

The prevalence of ITP in NHL (without CLL) in four large studies (1,850 patients) was 0.76% (range 0-1.8%), the prevalence of Evans's syndrome 0.16% (8.12-14.17).

Characteristics of individual patients with ITP in NHL

ITP in small lymphocytic lymphoma (SLL)

One case of ITP-SLL has been described.[18] This patient had ITP 12 months prior to a localized lymphoma of the liver

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(stage IIE). The ITP responded only transiently to steroids and splenectomy (SE), but a sustained complete remission of ITP and SLL was achieved after chemotherapy.

ITP in marginal zone lymphoma (MZL)

Seven MZL-patients associated with ITP have been reported, including four patients with MALT lymphoma,[19-22] two with splenic lymphoma with villous lymphocytes (SLVL)[23] and one with a nodular MZL.[24] The male to female ratio was 0.4. In three cases the ITP was diagnosed 1-10 years before diagnosis of lymphoma, in the other cases at the diagnosis of lymphoma. The MALT lymphomas were gastric lymphomas in three cases[19, 21, 22] and a lung MALToma in one case[20] (stage IE to IIE). All patients in whom the lymphoma was removed surgically (± subsequent chemotherapy)[19,21] or who received chemotherapy alone[22] achieved a CR of ITP. By contrast, most of these patients did not respond to steroids.[19,22,24] The two patients with SLVL achieved a CR of ITP after SE, which was sustained in one and transient in the other.[23]

ITP in hairy cell leukemia (HCL)

Two patients with HCL had an ITP. In one case, ITP was presented several months prior to diagnosis of NHL.[25] In another case, ITP developed after the diagnosis of lymphoma. This patient had received prior treatment with pentostatin.[26] Both patients were refractory to steroids. One had a sustained CR (22 weeks+) after rituximab[26] and one after splenectomy.[25]

ITP in lymphoplasmacytic lymphoma, Waldenström disease

Three cases of associated ITP were reported,[27-29] all were male. ITP preceded the lymphoma in one[29] and was concurrent in the other two. In two cases, an IgM antibody to platelets could be demonstrated, but the specificity could not be defined. None of the patients achieved a complete remission with conventional ITP-treatments (steroids, HD-IgG, splenectomy).

ITP in other low-grade lymphomas

An association of ITP and mantle cell lymphoma was reported in one case.[30] This patient had a partial remission after rituximab as first line therapy. In an original series of 171 cases with mantle cell lymphoma in our institute we found no case of an associated ITP. We have observed one female with an association of ITP and follicular lymphoma (the only patient with ITP among 81 consecutive patients with follicular lymphoma in our centre). ITP was diagnosed four years prior to the diagnosis of lymphoma and responded to prednisone with a sustained complete remission.

ITP in myeloma

The association of ITP-myeloma was reported in five cases (three male, two females).[31-32] In two cases ITP occurred 15 months and five years prior to the diagnosis. All patients had IgG myeloma (three lambda, two kappa). Four patients had a response of ITP to steroids and/or HD-IgG, but response was usually not sustained. There were no or only minor responses of ITP after chemotherapy.[31] One patient had a sustained PR after splenectomy.[32]

ITP in aggressive B-cell lymphomas

In 10 cases an aggressive B-cell lymphoma was associated with ITP. The male/female ratio was 2.3.[24,33-40] In three cases ITP occurred four, 18 and 46 months prior to the diagnosis,[24,34-35] in five cases concurrently with lymphoma[33,36,38-40] and in two after diagnosis (and chemotherapy).[35,37] Nine patients had DLCL, in one the histological diagnosis was not specified.[37] Six of the patients with DLCL had a primary extranodal lymphoma (Stage IE or IIE) of the adrenals,[33,38,40] heart,[37] kidney[39] or mesentery.[36] Only one patient (ITP before lymphoma) had a CR of ITP after steroids,[35] all the others had only partial or no responses. Two patients with adrenal lymphoma[40] and one with kidney lymphoma[39] achieved a sustained CR after surgery/splenectomy or chemotherapy and two[37-38] achieved a PR of ITP after chemotherapy.

ITP in T-cell lymphomas

In the literature, ITP was reported in only three cases with T-cell lymphomas.[41-43] Lymphoma diagnoses were hepatosplenic T-cell lymphoma in two cases[41-42] and highly malignant T-cell lymphoma.[43] In all cases, ITP was diagnosed 1.5-4 months before lymphoma. Only 1 patient had a sustained CR after steroid monotherapy.[43] Two patients received chemotherapy one of whom achieved a sustained CR and the other a tCR.

In an original series of 40 patients with peripheral T-cell lymphoma in our institute we found no case of ITP.

A renal transplant patient with severe bleeding tendency due to an antibody to GP IIB/IIIA without thrombocytopenia (acquired thrombasthenia) was reported by Tholouli *et al*.[44] Acquired thrombasthenia was successfully treated with cyclophosphamide, but the patient later developed AIHA and an angioimmunoblastic lymphoma. A similar case of acquired thrombasthenia was reported by Kubota *et al*.[45] after a malignant lymphoma of the stomach. The patient later became thrombocytopenic along with recurrence of lymphoma.

ITP after autologous stem cell transplantation (ASCT)

ITP occurred in eight patients after autologous stem cell transplantation in a heterogeneous group of NHL (two follicular lymphomas, one mantle cell lymphoma, two DLCL, one T-cell rich B-cell lymphoma, one Burkitt lymphoma and two highly malignant T-cell lymphomas).[46-48] The male/female ratio was 1.0 and the median age 45 years. All underwent peripheral stem

cell transplantation, two in CR and six in PR. ITP (including one Evans's syndrome) occurred after a median of five months (range 1-31 months). With one exception,[48] all patients were in CR at onset of ITP. The platelet counts ranged from 1,000 to 21,000/μL (median 7,000/μL). The megakaryocytes in the bone marrow were normal in four and decreased in two cases. Antibodies against GP IIB/IIIA were found in two patients. All except the patient with relapse responded to steroids and achieved a sustained CR after steroids alone or after SE.[46] Only one with ITP in relapse of lymphoma died.

Discussion

Non-hematologic autoimmune diseases are common and often precede the diagnosis of lymphoma.[1-3,14,49] Among the hematologic autoimmune disorders, AIHA is more common than ITP while in CLL, AIHA was 3.3 times more common than ITP (8-11). Both are less frequent in non-CLL– NHL and AIHA was only approximately twice as frequent as ITP (AIHA 1.57%, ITP 0.76%).[8,12-14,17] In Hodgkins' disease, AIHA and ITP were less common and equally frequent (AIHA 0.52, ITP 0.79%).[8,12,51,52] (Table 1)

We analyzed 33 cases of ITP and NHL reported in the literature (including one unreported case from our department). This is about one third of the number of reported cases of AIHA and NHL (n= 86).[4] While cases of AIHA and ITP were reported in a similar relative frequency in MZL, HCL, myeloma and DLCL there was a large difference in follicular lymphomas, T-cell lymphomas and lymphoplasmacytic lymphoma (Table 1). The dominant types of lymphomas in rheumatoid arthritis are DLCL and lymphoplasmacytic lymphoma,[1,53] MZL and MALT lymphoma are more common in Sjögren's syndrome and Hashimoto thyreoiditis.[1,3] Patients with celiac disease have a highly increased risk of gastrointestinal and T-cell lymphomas.[1]

The prevalence of ITP in lymphoma studies was 0/92 in myeloma,[8] 4% in MZL (54), 1.2% in follicular lymphomas (our department), 3.8–10% in makroglobulinemia,[10,28,55] and 9% in mantle cell lymphoma.[56] In T-cell lymphomas a prevalence of 11.1%[57] and in AILD prevalence of 24%[58,59] of thrombocytopenias was reported, but pathogenesis was not determined (Table 2 and 3).

The diagnosis of idiopathic ITP is essentially based as previously described[60-63] and associated with bleeding symptoms.[64,65] Five of the patients died, but none from uncontrolled bleeding. Although cases of functional impairment of GP IIB/IIIA by anti-GP antibodies have been described in NHL,[44,68] a functional abnormality has not been observed in patients with NHL-ITP. NHL-ITP is more frequent in males (Table 1), in contrast to female predominance in idiopathic ITP.[64-67] The number of patients with ITP in subtypes of NHL was too small to evaluate prevalence according to gender. The study has provided some data on the pathogenesis of ITP. The findings of a production of a platelet antibody by an extranodal aggressive lymphoma[38] and the demonstration of IgM platelet antibodies in lymphoplasmacytic lymphoma[27] support the assumption that in some cases the platelet antibody is produced by lymphoma tissue itself. Idiopathic ITP, ITP in CLL and ITP preceding NHL respond well to steroids, high dose immunoglobulin and/or splenectomy.[60,69] By contrast, ITP, which occurs at or after diagnosis of NHL, usually shows a poor response to these treatments (Table 3).[19,22-24,26,27,29,31,33,35,38,70,71] No sustained complete remissions after steroids alone were documented in these patients.

Table 1. Autoimmune hemolytic anemia, autoimmune thrombocythemia, and Evans' syndrome in various non-Hodgkin's lymphoma-subtypes.

Non-Hodgkin's lymphoma subtype	*AIHA*	*ITP*	*Evans's syndrome*
Small lymphocytic lymphoma	0	1	0
Follicular lymphoma	12	1	0
Marginal cell lymphoma	14	7	0
Mantle cell lymphoma	0	1	0
Hairy cell lymphoma	6	2	1
Lymphoplasmacytic lymphoma	0	3	0
Multiple myeloma	10	5	0
High grade B-cell lymphoma	25	10	2
T-cell lymphoma	22	3	4
References	4	1-71,87	4,72-86

AIHA: autoimmune hemolytic anemia. ITP: autoimmune thrombocythemia.

Table 2. Autoimmune thrombocythemia in non-Hodgkin's lymphoma.

Sex (M/F)	21/12
Median age (range)	53 (8-88 years)
ITP prior to lymphoma	15
ITP at onset of lymphoma	13
ITP in the course of lymphoma	4
Bone marrow megakaryocytosis	20/23*
PA-IgG increased	9/10*
P-glycoprotein antibodies	4/5*

**Number of positive results/patient evaluated.*

Table 3. Treatment of autoimmune thrombocythemia in non-Hodgkin's lymphoma.

	Number of treatments	*CR*	*Transient CR*	*PR*	*NR*
Prednisone ± IgG	29	3	8	7	11
Splenectomy	16	6	4	2	4
Surgery and/or [antilymphoma [chemotherapy	20	11	1	2	6
Rituximab	4	2	1	1	0

CR: complete remission. PR: partial remission. NR: no remission.

On the other hand, sustained CRs were observed after surgical removal of the lymphoma[21] or after anti-lymphoma chemotherapy. More than a half (64%) of the NHL-ITP achieved a CR after anti-lymphoma treatment. Interestingly, ITP in myeloma did not respond to chemotherapy, but did respond to steroids and/or SE. Therefore, the optimal treatment of NHL-ITP may be different from the standard treatment. Only in SLVL may splenectomy be the first line treatment of choice, similar to AIHA.[4]

The pathogenesis and treatment of ITP following autologous stem cell transplantation for NHL seems to be quite different.[46-48] These usually severe thrombocytopenias respond well to steroids and some late spontaneous remissions were recorded similar to idiopathic ITP and ITP in Hodgkin's disease.[52] In contrast to CLL, ITP may have been triggered by treatment only in a few cases[26,37] since the majority of ITP occurred at the time of diagnosis of lymphoma or prior to diagnosis. We observed one patient in our institute with a severe ITP during a treatment with rituximab, fludarabin and cyclophosphamide. Therefore, patients suffering from B-CLL in association with ITP should have a personalized treatment program.[87] Any association of NHL and ITP which changes the prognosis of the patients should be studied carefully. Analysis of these cases may be useful for physicians dealing with these patients and may help select the best treatment option.

Authorship and Disclosures

The manuscript was read and approved by all co-authors and all persons listed as authors made a significant contribution to its content. The authors reported no potential conflicts of interest.

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