Clinical and laboratory characteristics of cyclic thrombocytopenia: an observational study

Cyclic thrombocytopenia (CTP) is a rare disease with less than 70 reported cases. The hallmark of CTP is a periodic fluctuation of the platelet count. The severity of thrombocytopenia and the duration of cycles may vary. In many patients the platelet nadir is low and consequently bleeding complications can occur.[1] In some patients thrombocytopenia is followed by rebound thrombocytosis with peak platelet counts well above the normal range, which may cause a hypercoagulable state.[2] Most CTP cases were reported to be idiopathic, *i.e.* without an underlying disorder.[3] The pathomechanisms are poorly understood and are likely heterogeneous. The majority of patients is female and an association with the menstrual cycle has been recorded.[4] Autoimmune platelet destruction, megakaryocytic hypoplasia or impairment of regulatory mechanisms of platelet production are potential pathomechanisms.[3] CTP is often misdiagnosed as immune thrombocytopenia (ITP) and is only taken into consideration when ITP-specific treatments have repeatedly failed. A specific treatment for CTP does not exist. A beneficial effect of danazol, female hormones or cyclosporine A (CsA) has been reported in a handful of patients.[5-7] The long-term course of CTP is obscure.

We report nine patients with CTP who were diagnosed and managed at the coagulation clinic of the Department of Medicine I, Medical University of Vienna, Austria (eight patients) and at the Clinic of Hematology, Clinical Center of Serbia, Belgrade, Serbia (one patient). The study was approved by the ethics committee of the Medical University of Vienna. At the time of diagnosis, the patient age ranged from 36 to 65 years (Table 1). All patients except one were female and all were initially diagnosed with ITP. The time interval between diagnosis of ITP and CTP ranged from three months to 10 years. To capture nadir and peak platelet counts for the estimation of the cycle duration, platelet counts were measured weekly over a period of at least one month. Accordingly, cycle duration ranged from 14 to 35 days. In all patients the platelet nadir and the peak platelet counts were less than 10 g/L and greater than 450 g/L, respectively (Figure 1). A relationship between CTP and the menstrual cycle was noted in one patient (patient 1). In one patient CTP occurred at week 11 of gestation during an otherwise uneventful pregnancy (patient 5). At presentation five patients had mucocutaneous bleeding and four patients were asymptomatic. The follow-up went from 18 months to more than 16 years. During the follow-up all patients suffered from mucocutaneous bleeding, two patients had hematuria and one patient had gynecological bleeding. One patient had a non-fatal intracranial hemorrhage at a time when her platelet count was 1 g/L. Eight patients, all female, had a disorder of the thyroid

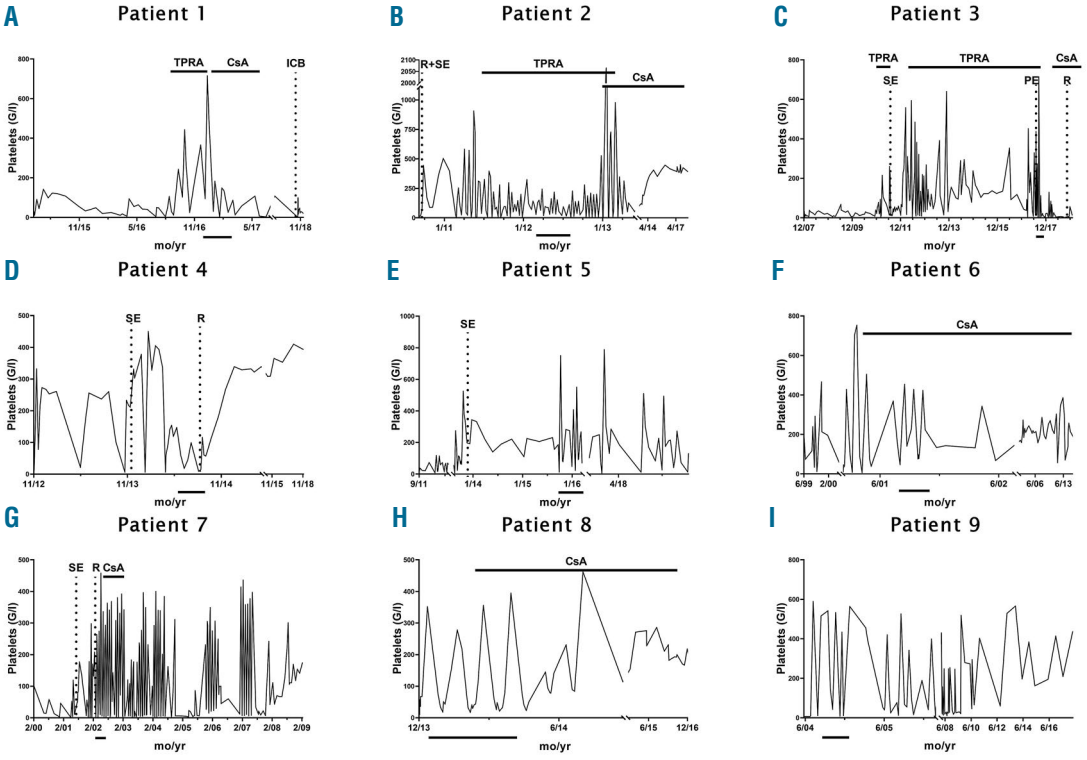

Figure 1. Course of platelet counts in nine patients with cyclic thrombocytopenia. Splenectomy (SE) (patients 2, 3, 4, 5 and 7) and treatment with a thrombopoietin receptor agonist (TPRA) (patients 1, 2 and 3) were ineffective. A durable remission was seen in six patients. In three patients the increase in platelet count was in association with cyclosporine A (CsA). Rituximab (R) treatment was followed by an increase in the platelet count in one (patient 4). One female each suffered from intracranial bleeding (ICB) (patient 1) or pulmonary embolism (PE) (patient 3). All patients were treated with corticosteroids without effect. Time of evaluation of cycle duration is indicated by a bar underneath the x-axis.

Table 1. Clinical and laboratory characteristics of nine patients with cyclic thrombocytopenia.

Pt #	Sex	Age at ID (yrs)	Time until ID (yrs)	Mean Cycle duration (days)	Bleeding at ID	Bleeding during follow-up	Comorbidities	Complications	TPO*	TCRR	Platelet antibodies
1	F	43	1.5	23	None	Intracranial Mucocutaneous Gynecological	Hypothyroidism	ICB	N/A	clonal	positive
2	F	55	2.5	14	None	Mucocutaneous	Hypothyroidism		N/A	clonal	N/A
3	F	65	10	28	Mucocutaneous	Mucocutaneous	Hypothyroidism	PE	no	clonal	positive
4	F	47	2.5	28	Mucocutaneous	Mucocutaneous	Euthyroid struma nodosa		N/A	N/A	N/A
5	F	36	4	26	None	Mucocutaneous	Hypothyroidism		N/A	none	N/A
6	F	57	1.5	28	Mucocutaneous	Mucocutaneous	Hypothyroidism, polymyalgia rheumatica	AML	yes	clonal	negative
7	M	41	3	24	None	Hematuria Mucocutaneous			yes	clonal	negative
8	F	53	0.3	35	Mucocutaneous	Mucocutaneous	Hypothyroidism, DM I	T-LGLL	N/A	clonal	negative
9	F	60	4	34	Mucocutaneous	Mucocutaneous	Euthyroid struma nodosa		N/A	none	negative

Pt #: patient number; F: female; M: male; ID: initial diagnosis of CTP; DM I: diabetes mellitus type I; ICB: intracerebral hemorrhage; PE: pulmonary embolism; AML: acute myeloid leukemia; T-LGLL: T-cell large granular lymphocytic leukemia; TPO: thrombopoetin; *indirect relationship between platelet count and TPO level; N/A: not assessed; TCRR: T-cell receptor rearrangement.

gland (hypothyroidism in six and euthyroid struma nodosa in two patients). ITP-specific treatments including corticosteroids (all patients), high-dose immunoglobulins (six patients), splenectomy (five patients), or thrombopoietin receptor agonist (three patients) failed. Rituximab treatment was followed by an increase in the platelet count in 1 of 4 patients (patient 4). A durable remission was seen in six patients between seven months and 9 years after CTP diagnosis. In three patients remission occurred during CsA therapy and in one patient after rituximab treatment. Two patients developed a hematological disease (acute myeloid leukemia and T-cell large granular lymphocytic leukemia) after 2.5 and 18 years, respectively. One patient suffered from pulmonary embolism at a time when she received a thrombopoietin receptor agonist and her platelet count was 437 g/L. Clonal T-cell receptor re-arrangement was found in six patients and anti-platelet antibodies in three patients. Cyclic fluctuations of leucocyte counts or hemoglobin levels were absent in all patients except one (patient 6). In two patients non-informative diagnostic bone marrow biopsies were performed at platelet counts of 8 g/L and 178 g/L, respectively, (patient 6) and of 36 g/L (patient 8). Thrombopoietin levels were measured in three patients at regular intervals. In two of them (patients 6, see reference and patient 7, Figure 2) a strong negative Spearman's correlation of -0.86 and -0.92, respectively, between platelet counts and thrombopoietin levels was found.[6]

We report several distinctive clinical and laboratory features important for the management of CTP patients. First and foremost, the diagnosis was made with a delay of many years in the majority of our patients. CTP patients have severe isolated thrombocytopenia, which seemingly resolves in response to corticosteroids and/or high dose immunoglobulins. Consequently, as the case in our patients, CTP is often misdiagnosed as ITP. Later on and in the absence of a durable "remission", patients are considered refractory and receive second and third-line ITP therapies.[3] In fact, 5 of 9 patients were splenectomized or were treated with rituximab or a thrombopoietin receptor agonist but without effect. An early diagnosis of CTP would preclude unnecessary exposure of patients to the risks associated with ITP treatment. However, as the diagnosis of CTP requires proof of periodic platelet count fluctuations in the absence of any therapy, an initial watch-and-wait strategy is hardly tolerable, neither for the patients nor for their doctors. Nevertheless, the diagnosis of CTP should at least be taken into consideration in patients non-responsive to standard ITP treatment, and should be excluded before patients are treated with more immunosuppression or splenectomy.

Some of our clinical findings, such as the relatively young age at presentation, female preponderance and cycle duration between two and five weeks, have already been described by others.[3] Interestingly, all our patients had severe thrombocytopenia with a platelet nadir of less than 10 g/L and rebound thrombocytosis with peak platelet counts above 450 g/L. In a review of the literature of 51 patients, less than a third had blood count deviations of similar severity.[3] The bleeding phenotype of our patients was usually mild which is in agreement with previous reports of CTP patients.[3] Notably, one patient suffered from intracranial bleeding at a platelet count of 1 g/L. Despite rebound thrombocytosis and sometimes excessively high platelet counts, we recorded only one thromboembolic event (pulmonary embolism at a platelet count of 437 g/L). This patient was treated with a thrombopoietin receptor agonist (eltrombopag), which may have further contributed to a thrombotic predisposition.

A striking finding was that eight patients, all females, had a disorder of the thyroid gland concomitantly with

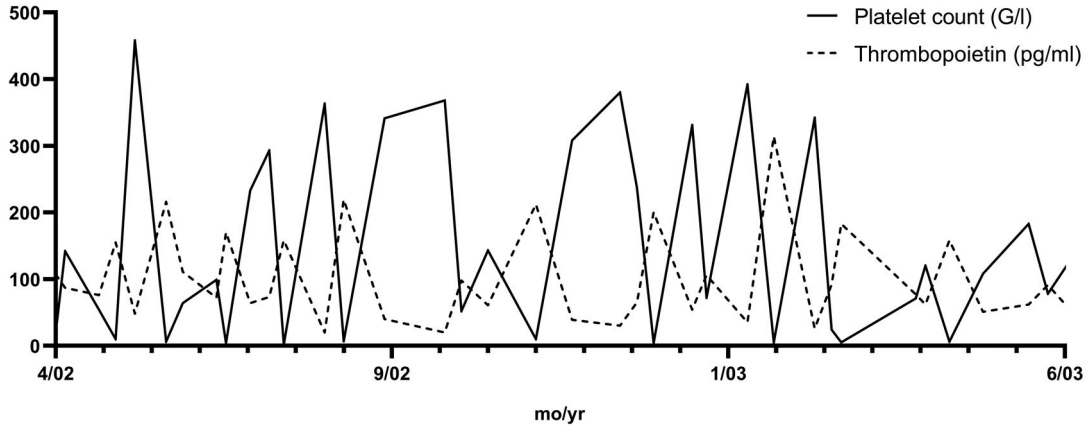

Figure 2. Relationship between platelet and thrombopoietin levels. A strong negative Spearman's correlation of -0.92 between platelet counts (solid line) and thrombopoietin (TPO) levels (dashed line) in a patient with cyclic thrombocytopenia (patient 7).

CTP. We do not believe that this is a chance finding but are unable to provide a ready explanation for the pathomechanism(s) behind this apparent coincidence. Two of these patients had antibodies to thyroid proteins, but we do not have data on the remaining six patients. So we are unable to speculate on an eventual autoimmune background as the underlying pathomechanism. Until now, only hematologic malignancies were reported to be connected to CTP.[8,9] The fact that two of our patients developed such a malignancy is in line with this observation.

It is well known that ITP-specific treatment strategies are ineffective in CTP patients.[3] Accordingly, corticosteroids, high-dose immunoglobulin, splenectomy and thrombopoietin receptor agonists all failed in our patients. Following our previous finding that immunosuppression with CsA resulted in an increase in the platelet count,[6] we treated five subsequent patients accordingly. We recorded a durable remission with platelet counts above 100 g/L in three patients. Of interest, we also observed spontaneous remissions, *i.e.* remissions in the absence of any treatment, in two patients (patient 7 and 9) 6 and 8 years after CTP diagnosis, respectively.

With reagards to the pathophysiology, several mechanisms such as autoimmune platelet destruction, megakaryocytic hypoplasia and defects in processes that regulate platelet formation were put forward.[10-12] Also a hormonal or infectious etiology has been discussed.[3] In 2002, we reported a CTP patient with a clonal T-cell receptor re-arrangement and surmised that a clonal T cell-mediated process could be the underlying mechanisms of her disease.[6] Interestingly, we detected a clonal T-cell receptor re-arrangement in another five patients. Clonal T-cell receptor re-arrangement is usually found in neoplastic disorders involving the T-cell lineage 13 and, notably, one patient indeed developed T-cell large granular lymphocyte leukemia. An indirect relationship between platelet counts and thrombopoietin levels was found in two of these patients. Three of the six patients with a clonal T-cell receptor re-arrangement also had anti-platelet antibodies. These observations suggest that (i) auto-immune platelet destruction and defects in the regulation of platelet formation may also play a role in CTP and (ii) that pathomechanisms of CTP might not be mutually exclusive. We cannot convincingly comment on possibly underlying abnormalities of the bone marrow as we avoided biopsies at a low platelet count. A non-informative bone marrow was obtained in two patients at platelet counts of 8, 178 and 36 g/L, respectively, for diagnostic reasons. An infectious etiology of CTP is unlikely in our CTP patients as none of them suffered from clinically relevant infections.

Based on our findings obtained in the largest CTP case series reported so far, we conclude: (i) CTP has to be considered in patients with ITP and an absent response to ITP treatment; (ii) CTP predominantly occurs in women and is often associated with disorders of the thyroid gland; (iii) the bleeding phenotype is usually mild, but life-threatening bleeding can occur; (iv) some patients may develop a hematological malignancy; (v) CsA therapy is effective in some patients; (vi) remission rates are relatively high; (vii) a clonal T cell-mediated process could be an important underlying pathomechanism.

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