Bleeding signs due to acquired von Willebrand syndrome at diagnosis of chronic myeloid leukaemia in children

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Summary

A considerable proportion of patients with chronic myeloid leukaemia (CML) may present at diagnosis with high platelet counts. This may result in thrombosis or bleeding complications due to binding of von Willebrand factor (VWF) multimers to platelets. Paediatric CML is very rare and no systematic investigation on clinical complications of elevated platelets has been reported. Data on platelet count and associated haemostaseological complications were retrospectively analysed in a cohort of 156 children with CML. Fifty-one percent (81/156) patients presented with thrombocytosis (platelet count > 500 × 109/l), and were extreme (>1 000 × 109/l) in 23/156 (16%). There were no cases of thrombosis but mild bleeding signs were present in 12% (n = 9) children with thrombocytosis. Bleeding occurred without correlation to elevated platelet counts and was associated with reduced large VWF multimers, indicating a diagnosis of acquired von Willebrand syndrome (AVWS), which resolved after initiation of CML treatment. Patients with paediatric CML frequently exhibit high platelet counts not resulting in thrombosis. In patients with thrombocytosis mild bleeding signs due to a low percentage of large VWF multimers can be demonstrated. AVWS may be underdiagnosed in paediatric CML (ClinicalTrials.gov NCT00445822, 9 March 2007).

Keywords: paediatric CML, thrombocytosis, high platelet count, acquired von Willebrand Disease, von Willebrand Multimers.

Chronic myeloid leukaemia (CML) is a proliferative clonal disorder originating from a haematopoietic stem cell (Hehlmann & Hochhaus, 2007). The cytogenetic hallmark, the Philadelphia chromosome (Ph+) harbouring the underlying reciprocal translocation t(9;22)(q34;q11-2) and the consecutive formation of the BCR/ABL1 fusion oncogene sharply separates CML from other myeloproliferative neoplasms (MPNs) (Thiele et al., 1999; Molica et al., 2017). Clinically, this leukaemia is characterized by splenomegaly and extreme leucocytosis resulting from the expansion of the myeloid cell compartment with presence of the entire spectrum of granulopoiesis, basophilia and eosinophilia in the peripheral blood. The BCR-ABL1 rearrangement also can be demonstrated in megakaryocytes from the vast majority of CML patients (Thiele et al., 1997) and expansion of the megakaryocytic compartment resulting in thrombocytosis may also contribute to diagnosis (Bleeker & Hogan, 2011; Chiarello et al., 2011).

CML typically manifests in the sixth decade of life and thrombocytosis, defined as a platelet count >500 × 109/l – and in individual cases this can be more than 1 000 × 109/l – is observed in 30% to 50% of adult CML patients (Cortes et al., 2005). However, thrombotic or bleeding complications are rare. Even with extreme thrombocytosis at diagnosis –defined as platelet count >1 000 × 109/l – it is reported that the incidence of complications is in the range of 1% to 10% (Schafer, 1984; Sorà et al., 2014; Liu et al., 2017; Sora et al., 2018). CML in childhood is a rare malignancy, representing less than 2% of all paediatric leukaemia cases (Chang et al., 2003; Millot et al., 2005; Suttorp & Millot, 2010; Suttorp et al., 2012; Hijiya et al., 2016). In Caucasians in the first two decades of life the age-specific incidence is 0.7–1.4, with a lower incidence reported in the Indian and Asian populations (Suttorp & Millot, 2010; Ganesan & Kumar, 2016). As CML in children occurs much less frequently than in adults, the question arises as to whether the biology and associated complications differ from adults with CML (Gassas et al., 2005; Hijiya et al., 2016; Hussein et al., 2018; Hijiya & Suttorp, 2019). So far, no data on bleeding symptoms or
thrombocytosis in association with platelet counts have been reported from larger cohorts with paediatric CML.

The bleeding disorder of acquired von Willebrand syndrome (AVWS) must be separated from the inherited type of von Willebrand disease (VWD) (Schnepfenheim, 2011; LEE-Beek & Eikenboom, 2016; James et al, 2016). As no single test can reliably confirm or exclude AVWS, the diagnosis may be challenging and must include a bleeding history of other family members (Tiede et al, 2011; Stockschlaeder et al, 2014; Maurer et al, 2015). The diagnosis of AVWS is usually based on the laboratory parameters typical for inherited VWD in the absence of a family history of bleeding (Federici, 2008). AVWS is usually associated with an underlying disorder and characterized by any qualitative structural or functional defects of von Willebrand factor (VWF), which may be the consequence of autoimmune, cardiovascular, malignant proliferative or other disorders, resulting in an increased risk of bleeding (Schnepfenheim & Budde, 2011; James et al, 2016). Pathophysiologically, VWF abnormalities in AVWS result from antibody-mediated clearance or functional interference, increased shear stress followed by proteolysis, or adsorption to surfaces of transformed cells or platelets. Sequestration of VWF high-molecular weight (HMW) multimers due to adsorption to platelets has been described in patients with AVWS (Budde et al, 1993; Budde & van Genderen, 1997).

There are some reports on single cases, but no article has systematically investigated AVWS in paediatric patients with CML at diagnosis presenting with thrombocytosis (Mccarthy et al, 1991; Byun et al, 2014; Verma et al, 2015; Huho et al, 2018). Therefore, in order to fully understand the clinical characteristics and potential haemostasological problems, we retrospectively reviewed and analysed the clinical information on paediatric patients with CML and associated thrombocytosis enrolled into a large paediatric phase 3 trial on upfront therapy with the tyrosine kinase inhibitor (TKI) imatinib (Suttrop et al, 2018).

Patients and Methods

Study Design

Children younger than 18 years diagnosed with previously untreated Ph + CML were eligible for this study. The protocol was approved by the ethical board of the Medical Faculty of the Technical University of Dresden (ethical vote # EK282 122006), registered with Clinical-Trials.gov (NCT00445822) and conducted in accordance with the Declaration of Helsinki. Written informed consent was provided by the patients’ legal guardians. An age-adapted written explanation was provided to the children and, if appropriate, written consent was given. Information concerning history of the patients, performance status at diagnosis, clinical findings including bleeding signs, peripheral blood and bone marrow analysis, cytogenetics, molecular analysis, blood chemistry, treatment applied and side effects observed was collected from participating centres using standardized forms to be filled in at diagnosis and for follow-up in 3-months intervals.

Due to the rarity of CML in childhood, in case of a newly diagnosed patient, treatment centres were asked to seek telephone counselling from the study chair. In case of presentation with bleeding signs and thrombocytosis, advice was given to extend routine coagulation testing by determination of the plasma concentration of the VWF antigen (VWF:Ag), an activity test to determine the VWF-platelet binding, such as VWF ristocetin cofactor activity assay (VWF:RCO) or VWF collagen binding (VWF:CB) or, if available, the VWF glycoprotein Ib binding (VWF:GPIbR), the ratio calculations (VWF:RCO/VWF:Ag, VWF:CB/VWF:Ag, VWF:GPlbR/VWF:Ag), factor VIII activity (FVIII:C) followed by the analysis of VWF multimers by gel electrophoresis. These extended laboratory tests were performed either in-house if offered or sent to a specialized commercial laboratory.

Results

Patients’ characteristics

A total of 156 patients (female n = 65; male n = 91) with a median age of 13-2 years (range 1-3–18) were recruited into study CML-paed II. The disease stage was chronic phase CML, accelerated phase CML and blast phase CML in 146, 3 and 7 patients, respectively. The haematological findings of the total cohort are reported in Table I. More details on CML and patients’ status at diagnosis, treatment applied and overall outcome have been reported elsewhere (Suttrop et al, 2018).

Thrombocytosis, by definition of a platelet count ≥ 500 × 10⁹/l, was diagnosed in 81 out of 146 patients (55.5%) from the cohort of patients in chronic phase. Forty-two patients exhibited platelet counts in the range of 500–750 × 10⁹/l, 14 patients in the range of 751–999 × 10⁹/l and, in 25 patients, the platelet counts ranged from 1000–2 784 × 10⁹/l. Data on clinical findings at diagnosis in 8 patients with thrombocytosis were inconsistent or missing, resulting in exclusion of these patients. Bleeding signs were present in 9 out of the 73 remaining patients (12%) with thrombocytosis and in 3 out of 65 patients (4.6 %) with regular platelet counts (range 151–497 × 10⁹/l; median 347 × 10⁹/l). The 3 patients in the cohort with regular platelet counts all suffered from retinal bleeding at diagnosis and,

| Leucocyte count [×10⁹/l] | Haemoglobin [g/l] | Platelet count [×10⁹/l] |
|--------------------------|------------------|--------------------------|
| Mean                     | 256              | 99                       | 639                       |
| Median                   | 205              | 96                       | 483                       |
| Range                    | 5.7–1 038       | 51–162                   | 75–3 054                  |
in addition, presented with rather high white blood cell counts (Case 1: 15-year-old female, 386 × 10⁹/l; Case 2: 14-year-old male, 402 × 10⁹/l; Case 3: 14-year-old male, 509 × 10⁹/l), which might have contributed to rheological problems. Bleeding signs in the cohort with elevated platelet counts (see Fig 1) comprised multiple haematomas after trivial trauma (n = 6, median 640 × 10⁹/l, range 510–1 389), retinal bleeding with blurred vision (n = 1, 669 × 10⁹/l), menorrhagia (n = 1, 1 213 × 10⁹/l) and prolonged bleeding for four days after tooth extraction (n = 1, 1 296 × 10⁹/l).

In four out of 9 patients with thrombocytosis (Patient 34, retinal bleeding; Patient 60, menorrhagia; Patient 64, prolonged bleeding after tooth extraction; Patient 67, skin bruising), extended laboratory analysis towards the direction of AVWS was performed. In the remaining five patients, the bleeding signs of skin bruising were interpreted as of minor importance from a clinical viewpoint not requiring additional diagnostic approaches once specific treatment of the underlying CML had been started with imatinib.

In the four patients investigated, the absolute values of VWF:Ag and FVIII:C remained in the normal range while the VWF:RCo/VWF:Ag and VWF:CB/VWF:Ag ratios were decreased. These patients also exhibited a significant loss of the high molecular weight VWF multimers in the plasma, which resolved once the platelet count had lowered in response to imatinib treatment. A typical response curve, as observed in Patient 64, treated at the authors institution is shown in Fig. 2.

Discussion

It is generally reported that thrombocytosis in adult CML patients has no close relationship with haemorrhagic and thrombotic events. When single centre studies investigated the episodes of haemorrhagic and thrombotic events, 22 out of 85 (26%) adult Chinese CML patients were assigned into CML with thrombocytosis but only one patient was detected with thrombosis at diagnosis, and no case with bleeding was observed (Liu et al, 2017). In an analysis from a single Italian centre, only one out of 100 adult CML patients developed thrombosis at diagnosis, and no history of bleeding was reported (Sorà et al, 2014). But when the same authors initiated a multicentre study in Italy, extreme thrombocytosis (platelet count >1 000 × 10⁹/l) was identified in 87 of 1591 adult CML patients representing an estimated frequency of 5-5% (Sora et al, 2018). At diagnosis, 9 out of these 87 (10-3%) patients had haemorrhagic or thrombotic complications, with severe grade in three individuals only. Thus, thrombocytosis may occasionally add to the array of clinical manifestations and increase morbidity as well as mortality of CML in adults (Rice & Popat, 2005; Verma et al, 2015; Jain, 2015).

In the cohort presented here, thrombocytosis (platelet count ≥ 500 ×10⁹/l) was diagnosed in 51% (81/1556) of the paediatric patients (Table I), which corresponds with the upper range of thrombocytosis (30-50%) reported in adults. However, extreme thrombocytosis (>1 000 × 10⁹/l) was present in 16% (25/156) of the paediatric patients, which is a ratio threefold times higher than reported in the Italian adult cohort (Sorà et al, 2018). In a French paediatric cohort, an almost identical proportion of 17-5% (7/40) children with extreme thrombocytosis was described (Millot et al, 2005). Several prognostic CML scoring systems in adults (e.g. Sokal, Hasford or EURO scores) consider thrombocytosis as an adverse risk factor (Pfirrmann et al, 2015) and thus the observation of a higher proportion of children with thrombocytosis matches well with other characteristics of CML, pointing to a more aggressive presentation of the disease when diagnosed in the first decades of life (Pemmaraju et al, 2012; Kalman et al, 2014; Gurrea Salas et al, 2015; Hijiya et al, 2016; Millot et al, 2017; Sutter et al, 2018).

Fig 1. Distribution of platelet counts in the cohort of 73 paediatric chronic myeloid leukaemia patients with a platelet count ≥ 500 × 10⁹/l. Cases with associated bleeding signs are marked with an asterix and the type of bleeding symptom is indicated.
Besides CML, Philadelphia chromosome-negative myeloproliferative neoplasms (MPN, polycythaemia vera [PV], essential thrombocythaemia [ET], primary myelofibrosis [MF]) are associated with thrombotic events occurring frequently at unusual sites (portal and splenic veins, mesenteric arteries, cerebral sinuses). While early reports attributed thrombosis to functionally abnormal erythrocytes, thrombocytes and leucocytes (Pearson & Wetherley-Mein, 1978), more recent findings focused on the role of a pro-inflammatory MPN milieu and the blood vessel endothelium interacting with qualitatively abnormal blood cells, all of which may express qualitatively or quantitative altered cell adhesion molecules (Bar-Natan & Hoffman, 2019). Like in CML, the thrombotic risk in patients with ET is rather not related to the degree of thrombocytosis, as those patients with very high platelet counts -including minors (Rolf et al., 2010)- exhibit a higher bleeding tendency due to the development of acquired VWD (Vannucchi & Barbu, 2007).

Elevated platelet counts are a well-known cause for AVWS associated with abnormal VWF multimer distribution in the blood plasma (Budde et al., 1993; Budde & van Genderen, 1997; Federici, 2008). According to the registry of the International Society of Thrombosis and Hemostasis (ISTH), myeloproliferative disorders represent 15% of the underlying reasons for AVWS (Federici et al., 2000). It was demonstrated a long time ago that adult CML patients in chronic phase (but not in blast phase) had a significantly lower percentage of large VWF multimers than normal controls (Tatewaki et al., 1988). In single patients with CML an IgG inhibitor recognizing the GPIb binding site(s) on VWF could be characterized (Mohri et al., 1996). But, to the best of our knowledge, no investigations on AVWS in children with CML have been published so far. It is likely, however, that AVWS in paediatric CML is underestimated because its diagnosis remains laborious and the bleeding symptoms seem to be mild.

The symptoms of AVWS include soft tissue bruising, epistaxis, gingival bleeding, gastrointestinal or genitourinary bleeding and menorrhagia, which is well in line with the bleeding signs observed in the paediatric cohort described here. Following adsorption of high-molecular weight VWF multimers to platelets, sequestration and proteolytic cleavage of the unfolded multimers due to shear stress is the underlying pathophysiological principle, as demonstrated in patients with thrombocytosis due to haematological neoplasms as well as in reactive thrombocytosis (Budde et al., 1984; Federici et al., 1993; Tsai et al., 1994; Wu et al., 2010).

Initiation of imatinib as targeted treatment of CML as the underlying condition of AVWS lowers the elevated white cell and platelet counts, as demonstrated exemplarily in Patient 64 (Fig. 2). This is paralleled by an increase of the VWF multimers, thus resulting in remission of the AVWS. Because this restitution will require two to four weeks, intermediate treatment options include desmopressin or, in severe cases of bleeding, VWF-containing concentrates, intravenous immunoglobulin or recombinant coagulation factor VIIa (Tiede et al., 2011). However, none of these interventions was required in children with CML in this cohort.

In conclusion, we here describe, for the first time, an analysis of haemostaseological findings associated with high platelet counts in newly diagnosed paediatric patients with CML. In contrast to reports on CML in adults, a threefold higher proportion of children and young adolescents with

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Fig 2. Gel electrophoresis densitogram pattern of VWF multimers in patient #64 at diagnosis and at two time points (3 weeks, 8 weeks) after initiation of treatment with imatinib in comparison to a healthy control A) Thrombocytosis at diagnosis and at week 3 is associated with a pathologically decreased ratio of VWF:CB/VWF:Ag. B) The densitogram of the gel electrophoresis demonstrates the missing fraction of high molecular weight multimers (arrow solid line) and an increase in the fraction of low molecular weight multimers (arrow dashed line). When platelet counts had normalized after 8 weeks also a normal pattern of VWF multimers could be observed. Abbreviations: VWF:Ag: Von Willebrand factor antigen; VWF:CB: von Willebrand factor collagen binding activity; path: pathological. [Colour figure can be viewed at wileyonlinelibrary.com]
CML (16%) exhibited extreme thrombocytosis (<1 000 × 10^9/L). However, no thrombosis was observed in this paediatric cohort while 12% of patients with thrombocytosis presented with mild bleeding signs corresponding to the spectrum of bleedings signs observed in AVWS. Excluding cases with mild skin bruising from an in-depth haematostaseological analysis, paediatric patients as previously described in adults - exhibited a significantly lower percentage of high molecular weight VWF multimers. Under treatment with the tyrosine kinase inhibitor, imatinib, these findings normalised when white blood cell and platelet counts lowered.

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Authors’ Contributions

The concept of this retrospective investigation was developed by all authors. BSL and FP performed the data collection and patient care, OT and RK supervised the laboratory analyses, and RK together with MS wrote the first draft of the typscript and critically revised all comments. All authors revised the text and approved the final version.

Conflicts of Interests

RK, BSL, FP, and OT have no competing interests. MS has received research grants (institutional), lecture fees, and honoraria for membership on advisory boards from Novartis, Bristol-Myers-Squibb, and Pfizer.

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Ethics approval and consent to participate

The protocol was approved by the ethical board of the Medical Faculty of the Technical University of Dresden (ethical vote # EK282122006), registered with Clinical-Trials.gov (NCT00445822) and conducted in accordance with the Declaration of Helsinki. Written informed consent including agreement on encrypted data publication was provided by the patients’ legal guardians. Age-adapted written explanation was provided to the children and if appropriate written consent was given.

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