Heparin-induced thrombocytopenia associated with thrombotic microangiopathy

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Summary
Some cases of thrombotic microangiopathy (TMA) are refractory to plasma exchange therapy (PE) with persistence or recurrence of thrombocytopenia. We report two patients suffering from TMA of different aetiologies (associated with disseminated malignancy, typical haemolytic uraemic syndrome) with recurrent or persistent thrombocytopenia despite adequate therapy including PE. Since both patients were exposed to unfractionated heparin, heparin-induced thrombocytopenia (HIT) was suspected as a cause. Pre-test probabilities for HIT were intermediate. ELISA for PF4/heparin antibodies was strongly positive in both cases, and HIT was confirmed by heparin-induced platelet activation assay. Anticoagulation with lepirudin was initiated, with subsequent rapid increase of the platelet count. TMA might represent a predisposition for HIT. This could be due to TMA-related platelet activation with increased PF4 release. In TMA patients exposed to heparin and with refractory or rapidly recurrent thrombocytopenia HIT should always be considered as a possible cause.

Schlüsselwörter
Thrombotische Mikroangiopathie, TMA, Thrombozytopenie, Heparin, Heparin-induzierte Thrombozytopenie, HIT

Zusammenfassung

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Thrombotic microangiopathies (TMA) are a heterogeneous group of disorders, with Coombs-negative microangiopathic haemolytic anaemia and thrombocytopenia as a common hallmark (18).

- Primary TMA include
  - thrombotic thrombocytopenic purpura (TTP), either congenital or acquired, and
  - the haemolytic uraemic syndrome (HUS), either typical after infection with Shiga toxin-producing bacteria or atypical due to complement dysregulation.

- Secondary TMA are associated with a variety of diseases and conditions, e.g. disseminated malignancy, allogeneic haematopoietic stem cell transplantation, systemic lupus erythematosus, certain drugs such as ticlopidine or cyclosporin A, HIV infection, or pregnancy (4, 5, 8, 10).

TMA-related mortality is exceedingly high, and immediate plasma exchange (PE) with fresh frozen plasma (FFP) is the initial therapy of choice (13, 23).

However, its efficacy may vary substantially. PE is generally more favourable in primary TMA but often unsuccessful in secondary TMA. For example, TMA associated with malignancy or haematopoietic stem cell transplantation is in most cases unresponsive to therapy with a high mortality (5, 10, 15).

Some patients are refractory or relapse despite adequate therapy. A considerable proportion of patients suffering from acquired TTP caused by inhibitory autoantibodies to the von Willebrand factor-clearing protease ADAMTS-13 show an exacerbation of TMA activity and a decrease of
the platelet count around day 7–10 of PE. This corresponds with an increase of the autoantibody titer frequently observed at this time (inhibitor boosting) (22). However, resistance or recurrence of TMA and thrombocytopenia can be mimicked by other conditions not directly related to TMA activity, e.g. systemic infections (2). We report two patients suffering from TMA who despite adequate therapy showed a recurrent or persistent thrombocytopenia which was attributed to heparin-induced thrombocytopenia (HIT).

HIT is an immune-mediated prothrombotic complication of heparin therapy. It is typically observed 5–14 days after the initiation of heparin administration, or as early as on the first day in case of a recent exposition to heparin (6). The interaction of heparin and platelet factor 4 (PF4) generates a new antigen which induces antibody formation. Several factors contribute to its immunogenicity and the risk of HIT development. These include the stoichiometric concentrations of heparin and PF4, with prophylactic heparin concentrations being associated with a higher risk than pharmacologic concentrations (7, 25). Other factors are the size, amount, and stability of PF4/heparin complexes (6). The type of heparin is of major importance, with a higher risk associated with unfractionated than with low molecular weight heparin (27). The prevalence of HIT is also determined by the patient population, with a significantly higher risk in patients undergoing major surgery such as cardiac or orthopaedic surgery or suffering from extensive trauma as compared with minor surgery or non-surgical patients (16, 25, 28). The higher risk in major surgery or extensive trauma corresponds with an increased platelet activation and release of PF4 from alpha granules (12) facilitating the formation of PF4/heparin complexes.

In the patients described here HIT was triggered by exposition to unfractionated heparin, and was probably favoured by TMA-related platelet activation and PF4 secretion.

**Patients and results**

**Patient 1**

A man (age: 78 years) presented with acute TMA. Activity of the von Willebrand factor-cleaving protease ADAMTS-13 as measured with FRETS-VWF73 assay (11, 14) was normal (84%). Daily PE with FFP was initiated without delay, and was accompanied by the administration of corticosteroids. Because of acute renal failure regular haemodialysis was initiated on day 2. Although disseminated prostate cancer was revealed in the course of the next days the patient responded surprisingly well to therapy, with a normalization of the platelet count after only four PE and reaching a maximum of 586 G/l.

However, this was followed by sudden recurrence of the thrombocytopenia with a decrease to a minimum of 84 G/l (Fig. 1a). Unfractionated heparin in non-pharmacological doses was administered during haemodialysis and for thromboprophylaxis. HIT was therefore suspected as a possible cause of the recurrent thrombocytopenia. Pretest probability for HIT was estimated to be intermediate using a validated score (24). ELISA for antibodies to PF4/heparin (GTI PF4 assay) was strongly positive (IgG 1.8 OD, clinically relevant cut off is around 1.3) (19). HIT was subsequently confirmed by heparin-induced platelet activation assay (HIPA) assay. There was no indication of a thromboembolic complication. Anticoagulation with the direct thrombin inhibitor lepirudin was started, and normalization of the platelet count to > 150 G/l was achieved within three days.

**Patient 2**

A woman (age: 55 years) was transferred from a regional hospital where she had presented with acute TMA. ADAMTS-13 activity was normal (64%). PE with FFP was started on day 1 and was accompanied by corticosteroids. Due to acute renal failure regular haemodialysis was initiated on day 2 and maintained for a total of 16 days. Prolonged thrombocytopenia was observed with 60 G/l on the day of transfer to the university hospital of Zürich (Fig. 1b). PE was terminated after 17 days when typical HUS was confirmed by the detection of Shiga toxin-producing E. coli in the patient’s feces. Because unfractionated heparin in non-pharmacological doses was administered during haemodialysis HIT was suspected as a possible cause of the prolonged thrombocytopenia. Pretest probability for HIT was estimated to be intermediate. ELISA for antibodies to PF4/heparin was strongly positive (IgG 2.7 OD), and HIT was subsequently confirmed by HIPA assay. There was no indication of a thromboembolic complication. Anticoagulation with lepirudin led to normalization of the platelet count to > 150 G/l within two days.

**Patient 3**

HIT was suspected also in a third patient but confirmation could not be obtained in this case. A woman (age: 30 years) presented with acute acquired TTP with severe ADAMTS-13 deficiency and an ADAMTS-13 inhibitor of > 2 BU. After three days of PE the platelet count had normalized, and PE was halted on day 6. Sudden recurrence of the thrombocytopenia was noted on day 8 with a minimum of 6 G/l but was no longer associated with severe ADAMTS-13 deficiency (Fig. 1c). Since unfractionated heparin was administered during PE, HIT was considered as a possible cause. Although pretest probability for HIT was low and the extent of thrombocytopenia was unusually pronounced, a particle gel immunoassay for PF4/heparin antibodies (ID PaGIA, Bio-Rad) was performed and was positive on two consecutive days. Subsequent daily PE was continued using lepirudin as an anticoagulant. A total of 60 PE as well as administration of intravenous immunoglobulin and of the anti-CD20 antibody rituximab were required to achieve remission. Unfortunately, a confirmatory functional assay (HIPA) was not performed and there are no suitable samples available for retrospective analysis.
TMA can be refractory or relapse rapidly, with prolonged or recurrent thrombocytopenia despite adequate therapy. Such a course may be attributable to the type of the underlying disease. For example, TMA associated with disseminated malignancy or with allogeneic haematopoietic stem cell transplantation rarely respond to PE (5, 15). Increase of the TMA activity can be another cause as observed in some patients with acquired TTP together with a boosting of ADAMTS-13 inhibitory autoantibodies during PE (22).

Besides this, refractoriness or relapse can be mimicked by conditions not directly related to the TMA activity such as systemic infections (2). Infections can preexist and also serve as a trigger of the acute TMA bout (3), or occur during PE and be facilitated by central venous catheters or corticosteroid treatment (9, 17, 20, 21). We describe two patients suffering from TMA of different aetiologies who showed a rapidly recurrent or prolonged thrombocytopenia despite PE. Since both patients were exposed to unfractionated heparin during haemodialysis and for thromboprophylaxis, HIT was suspected and was confirmed by ELISA for PF4/heparin antibodies and by HIPA assay (26).

It is uncertain whether the recurrent thrombocytopenia observed in a third patient suffering from acquired TTP is attributable to HIT or rather to an alternative mechanism. Refractory TTP would certainly be an obvious cause. However, ADAMTS-13 activity was no longer deficient when determined two days after recurrence of thrombocytopenia (Fig. 1c).

On the other hand, the extent of thrombocytopenia is unusual for HIT. Moreover, the ID PaGIA assay used as a screening for PF4/heparin antibodies has not a high positive predictive value for HIT (1), and confirmation of HIT by functional assay (HIPA) was not obtained.

We assume that several factors have promoted the development of HIT in the TMA patients described here. Comparable with the settings of major surgery or extensive trauma a strong activation of platelets is found in TMA (29) resulting in an increased PF4 release in a highly inflamma-
tory environment, thus facilitating the formation of PF4/heparin complexes. Also, exposition to unfractionated heparin during active TMA occurred with a dose that was probably optimal for the formation of PF4/heparin complexes (non-pharmacological heparin concentration).

Conclusion

TMA might represent a predisposition for HIT. As a consequence, HIT should always be considered as a possible complication in patients suffering from TMA who present with refractory or recurrent thrombocytopenia despite adequate therapy and who were recently exposed to heparin.

References