

Review / Revisão

## Coagulation abnormalities in acute promyelocytic leukemia

### *Alterações da coagulação associadas à leucemia promielocítica aguda*

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*Acute promyelocytic leukemia is frequently accompanied by coagulation abnormalities usually described as laboratorial disseminated intravascular coagulation, which is the main cause of morbidity and early mortality. Aberrant activation of the coagulation cascade and hyperfibrinolysis play an important role in the pathogenesis of bleeding diathesis, but their contribution varies from case to case. Here we review the main laboratorial findings and the recommended clinical management of coagulopathy associated with acute promyelocytic leukemia. Rev. Bras. Hematol. Hemoter. 2009; 31(Supl. 2):48-50.*

**Key words:** *Acute promyelocytic leukemia; coagulation; fibrinolysis; disseminated intravascular coagulation.*

#### Introduction

Acute promyelocytic leukemia (APL) is invariably associated with recurrent chromosomal abnormalities involving the receptor of retinoic acid (RAR). In about 98% of the cases the companion gene involved is the promyelocytic leukemia gene (PML), resulting in the PML-RAR $\alpha$  fusion gene and a chimeric protein with reduces sensitivity to retinoic acid. Nevertheless, pharmacological doses of all-trans retinoic (ATRA) can disrupt this resistance and lead to differentiation of leukemic blasts.<sup>1-7</sup> Consequently, protocols which associate ATRA and standard chemotherapy have become the standard in this disease and remission rates of almost 90% have been achieved.<sup>8,9</sup>

Clinically, a major aspect of APL is the presence of coagulation abnormalities and about sixty percent of patients present at least minor bleeding at diagnosis.<sup>10,11</sup> Before the availability of ATRA, from 10 to 30 percent of patients died early during treatment.<sup>11-13</sup> Despite the high cure rates reported, the coagulopathy is still the main factor responsible for morbidity in this disease<sup>14</sup> and the cause of early mortality.<sup>9</sup>

#### Laboratorial Hemostasis in APL

Most APL patients present at diagnosis with prolonged prothrombin time, partial thromboplastin time and thrombin time, hypofibrinogenemia, high D-Dimers and low platelet counts.<sup>15-18</sup> The thrombin-antithrombin complex (TAT) and fibrinopeptide A are elevated, which represent intravascular thrombin formation and activation of the coagulation cascade in vivo suggesting that a mechanism similar to disseminated intravascular coagulation (DIC) may be present.

Currently, there is evidence that APL blasts express tissue factor (TF) and secrete interleukin 1, inducing activation of the coagulation cascade.<sup>19-21</sup> Also, an alternative procoagulant, namely Cancer Procoagulant, which activates Factor X directly, is present in APL cells.<sup>22</sup> Despite this, some peculiarities are found in APL coagulopathy: the platelet half-life is normal,<sup>23</sup> and protein C and antithrombin plasmatic concentrations are normal,<sup>20,24</sup> different from classical DIC.<sup>25</sup> Moreover, clinical bleeding is disproportional to laboratorial data suggesting that different mechanisms may be involved.

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The detection of low levels of  $\alpha 2$ -antiplasmin,<sup>24</sup> an antifibrinolytic agent, implies that an hyperfibrinolytic state may be present.<sup>26</sup> Plasminogen activation inhibitor-1 (PAI-1) and lower levels of fibrinogen compared to DIC highlight fibrin lysis as an important mechanism in APL.<sup>26</sup> Moreover, thrombin activated fibrinolysis inhibitor is quantitatively normal, while classically in DIC, there is consumption of this factor.<sup>27</sup> Additionally, the promyelocytic leukemia cell line (NB4) can increase plasmin formation by 21 times *in vitro*.<sup>27</sup> Another interesting point is the over-expression of annexin II in APL cells.<sup>28-30</sup> Annexin II binds to tPA and plasminogen and improves plasmin activation by almost 200 times.

A third mechanism is involved in APL coagulopathy. The activity of some proteolytic enzymes is above normal and some of them can lyse fibrin. Elastase levels are raised,<sup>31</sup> and there is evidence that it breaks down fibrin. As fibrin degradation products have inhibitory effects on the coagulation cascade (specially fragment D-like), this proteolysis has an anticoagulation effect.

Therefore, APL coagulopathy is peculiar. Some laboratorial data may suggest DIC, but the bleeding signs are more intense than a hemostasis test could preview. There is evidence that activation of fibrinolysis and some proteases play an important role. Hence, the coagulation abnormalities are due to at least three pathways which can explain why bleeding is so significant in this disease.

### ATRA effects on hemostasis

After the introduction of ATRA in the clinical practice, an important improvement was observed in the evolution of patients.<sup>32-36</sup> Surprisingly, besides the expected effect on cell cycle, a remarkable improvement in several coagulation tests and reduction in bleeding diathesis were observed.<sup>35,36</sup>

ATRA treatment leads to normalization in plasminogen,  $\alpha 2$ -plasminogen inhibitor, fibrinogen, D-dimers, TAT and fibrinopeptide A concomitantly to a reduction in TF expression.<sup>15,20,36</sup> ATRA acts on the vascular endothelium and regulates cytokine and thrombomodulin expressions.<sup>15,20</sup> Curiously, there is an increase in tPA expression about 30 days after the beginning of treatment.<sup>36</sup>

### Patient management

A major concern when treating APL patients is the necessity of prompt ATRA administration on suspicion. This can partially revert the coagulopathy and improve outcomes. Concomitantly, an interesting point is to avoid classical chemotherapy regimens, which can lead to worsening of bleeding. Despite a growing understanding of the pathophysiology, no specific treatment has been proposed for coagulation abnormalities. Transfusions should keep platelet counts above 30-40 x 10<sup>6</sup>/ $\mu$ L and there is no consensus as to whether plasma and cryoprecipitate should

be used prophylactically. Leukocytapheresis must be avoided due to worsening in coagulation diathesis. There is no evidence that administration of antifibrinolytic drugs has any beneficial effect.

### Conclusion

APL is a standard for disease directed therapy. Survival is near 90% in some trials, but bleeding remains a major concern. Coagulation diathesis has multiple causes and can be summarized in three points: coagulation activation, fibrinolysis and proteolysis. An aggressive treatment once APL is suspected is the key to reduce morbidity and mortality.

### Resumo

*A leucemia promielocítica aguda (LPA) é geralmente acompanhada por anormalidades da coagulação usualmente descritas como coagulação intravascular disseminada e que são a principal causa de mortalidade precoce. A ativação anormal da cascata de coagulação e a hiperfibrinólise desempenham importante papel na patogênese da diátese hemorrágica, mas a contribuição de cada fator varia de caso a caso. Apresentamos aqui uma revisão dos principais achados laboratoriais e da recomendação para o manejo clínico da coagulopatia associada a LPA. Rev. Bras. Hematol. Hemoter. 2009;31(Supl. 2):48-50.*

**Palavras-chave:** *Leucemia promielocítica aguda; coagulação; fibrinólise; coagulação intravascular disseminada.*

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