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## Transplacental transmission of EDTA-dependent pseudothrombocytopenia

Sir,

Pseudothrombocytopenia (Pstp) is an *in vitro* laboratory finding usually associated with the use of EDTA in blood collection tubes; it may cause unjustified alarm in the patient and physician, sometimes leading to the use of unwarranted diagnostic procedures or treatment.[1] This rare phenomenon (1:1,000)[2] is related to *in vitro* platelet clumping caused by immunoglobulins (most often IgG) recognizing platelet antigens which are exposed on the membrane only in the presence of EDTA.[3] Over the past 12 years we have collected about 200 cases of Pstp, almost always discovered during routine hematologic tests and sent to us with the diagnosis of asymptomatic thrombocytopenia. The phenomenon is time- and temperature-dependent; once established, it seems to be permanent.[4] So far, a familial occurrence has never been documented. We describe a case of transient congenital Pstp in a baby born to a mother with Pstp. A 38-year old woman was found to have persistent severe thrombocytopenia by routine electronic blood counting; there was no history of antecedent or present bleeding tendency. The automatic platelet count on EDTA-anticoagulated sample was $20\times10^9$/L; a peripheral blood smear exhibited multiple large platelet clumps. Platelet count performed immediately after withdrawing the blood was $267\times10^9$/L; counts performed every ten minutes on the same test tube kept at room temperature showed a progressive reduction in platelet number , reaching the nadir at 4 hours. This phenomenon was absent in heparinized blood, and less evident when citrate or oxalate was used as the anticoagulant. We diagnosed EDTA-dependent pseudothrombocytopenia. The phenomenon was still present at a follow-up performed 1 year later. Six years later, the woman became pregnant and delivered a baby without complication. At routine examination, the newborn showed a platelet count of $23\times10^9$/L, in the absence of any bleeding tendency. Large platelet clumps were evident on the blood smear. A count from heelstick blood, immediately diluted in a buffer solution without EDTA, showed a platelet count of $430\times10^9$/L. After 1 month, the baby's platelet count was normal, even in the presence of EDTA. Repeat counts performed over the following months showed persistence of Pstp in the mother but absence of the phenomenon in the baby. This case documents transplacental transmission of the plasmatic factor, probably an IgG, responsible for Pstp. It also indicates the need to consider the likelihood of this phenomenon in neonates with asymptomatic thrombocytopenia in order to avoid inappropriate and potentially harmful treatments.

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***Key words***

*EDTA, pseudothrombocytopenia*

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## Acenocoumarol and 6-mercaptopurine: an important drug interaction

Sir,

Many drugs are known to interact with oral anticoagulants (OA),[1] but the greater part of the reported interactions refer to warfarin. Acenocoumarol is the most widely used coumarinic derivative used in Spain as an OA. 6-MP is a metabolite of azathioprine, both used as immunosuppressant drugs in a variety of autoimmune disorders. 6-MP decreases warfarin activity, and severe bleeding was described in a patient on long-term warfarin treatment after discontinuing azathioprine.[2]

**Table 1. Acenocoumarol requirements before, during and after 6-MP.**

| | *Pre-leukemia* | *X/95-VI/96* | *VII/96-XI/97* | *After XI/97* |
|---|---|---|---|---|
| INR | 3.3 | 1.9 | 3.4 | 3.4 |
| mg/week | 21 | 70 | 71 | 21 |

In this paper, we report an increased acenocoumarol requirement in a patient receiving 6-MP. The patient was a 53-year old woman with an aortic prosthetic valve and aorto-coronary by-pass. She was on long-term OAT with acenocoumarol (mean dose 21 mg/week and mean INR=3.3) since January 1992 until August 1995. Her treatment included captopril, isosorbide trinitrate and furosemide. The level of hypocoagulability was measured every four weeks using bovine thromboplastin ISI=0.98 (Thrombotest from Nycomed, IMMUNO, Barcelona, Spain) with a mechanical coagulometer AMAX CS-90 (from Grifols-Movaco, Barcelona, Spain) assisted by a computer program (Sintromac from Grifols, Barcelona, Spain). Her dose of acenocoumarol was adjusted according to the results which were expressed as the INR as recommended by the *Subcommittee of Standardization of the International Society on Thrombosis and Hemostasis*. She had a mean INR = 3.37. In August 1995 she was diagnosed as having acute promyelocytic leukemia. Induction of specific treatment was excluded because of her age and cardiac disease. OAT was stopped and heparinization and all-transretinoic acid (ATRA) were started and continued until the end of September. From October 1995 she received 6-MP 100 mg daily *p.o.*, methotrexate every two weeks i.v. and ATRA fifteen days every three months, for two years. During this time, liver damage was minimal (AST=60; ALT=70; total bilirubin = 1.2 mg/dL) and platelet count not less than $150\times10^9$/L. The level of hypocoagulability was, at that time, measured every two weeks. The dose of acenocoumarol was increased progressively from 21 mg/week when she started cytotoxic treatment to 70 mg/week in June 1996, with a mean INR=1.9. From June 1996 to November 1997, the patient maintained a mean INR=3.4 with a mean dose of 71 mg/week (see Table 1). When 6-MP was stopped, the patient continued receiving 70 mg/week for a week. At the end of this week, her INR had increased from 3 to 12. The acenocoumarol was stopped and reintroduced 24 hours later at her habitual dose (3 mg/day) without hemorrhagic complications.

Although the interaction of azathioprine or 6-MP with acenocoumarol is not established, studies in rats indicate that 6-MP increases prothrombin synthesis or activation[3] and decreases warfarin activity.[2,5] An increase in warfarin requirements can be interpreted as a prothrombotic state in patients with disorders requiring immunomodulatory therapy.[5,6] Our patient had a promyelocytic leukemia, known to cause a prothrombotic state. Our patient required a progressively increasing dose of acenocoumarol that she maintained during the remission period of the hematologic process; only when it finished, did she return to the normal requirements. In spite of the short life of acenocoumarol compared to warfarin, the increase of INR after stopping 6-MP was delayed, which suggests a metabolic interaction between 6-MP and OA, possibly induction of hepatic microenzymes activity, as seen with barbiturates.[5] According to the behavior of our patient, OA dosage (acenocoumarol or warfarin) should be reviewed no later than a week after ending azathioprine or 6-MP and the OA dose reduced to the amount before 6-MP treatment.

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## Autologous peripheral blood stem cell transplantation in a patient with multiple sclerosis and concomitant Ph+ acute leukemia

Sir,

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system in which T-cell mediated immune destruction of myelin is thought to be pathogenetically relevant.

Immunomodulating and immunosuppressive agents