Table 1. Plasma and urinary ET-1 levels, and plasma vWF activity in two relatives affected by PXE and in three other unaffected relatives. Plasma vWF activity was expressed as percentages of normal pooled plasma, the antigen levels of which were defined as 100%.

	Father (affected)	*Patient (affected)*	*Sister (unaffected)*	*Brother (unaffected)*	*Son (unaffected)*
Plasma ET-1 *(n.v. 0.5-1.2 pg/mL)*	2.78	2.98	0.98	0.67	2.66
Urinary ET-1 *(n.v. 0.3-1.2 µg/h)*	1.5	3.34	0.58	0.68	4.56
Plasma vWF activity	212%	188%	100%	98%	176%

ed by PXE, who, besides presenting all the required diagnostic criteria, also developed, as a rare complication of her disease, an atrial septal aneurysm. Both the patient's father and one of her brothers, who had died of acute myocardial infarction, had been diagnosed as having PXE, and her paternal grandfather was also supposed to have had it. Neither her mother nor any other relative from the materal lineage showed signs of the disease, thus suggesting a dominant autosomal inheritance. Two of the patient's brothers and her 15 year-old son do not present clinical evidence of PXE.

Endothelin-1 (ET-1), a potent vasoconscriptor, and von Willebrand factor (vWF), have been demonstrated to be markedly increased when the vascular endothelium is damaged.[3] Furthermore, some authors have suggested that both ET-1 and vWF could contribute to the progression of vascular lesions in patients with PXE.[4] Plasma and urinary ET-1 titers, and vWF plasma activity were titered in the two PXE patients and in their three clinically unaffected relatives using a commercial sandwich immunoassay technique (R&D Systems, Minneapolis, MN, USA),[5] and an enzyme-linked immunosorbent assay method, respectively (Boehringer-Mannheim Co., Milan, Italy).[4] The results we obtained (Table 1) showed a marked increased in ET-1 plasma and urinary titers and in vWF plasma activity not only in the affected individuals, but also in the patient's healthy son, despite his lack of clinical signs of PXE.

Although we cannot predict whether this boy will develop PXE during his lifetime, the increase in ET-1 and vWF titers might be the first biochemical fingerprint, of this still not clinically evident disease.

However, the central question still remains unanswered; as a matter of fact, if the patient does go on to develop PXE, we do not know whether the observed early increase in ET-1 and vWF is the primary insult leading to overt PXE or simply the first sign of a still subclinical disease.

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Severe immune thrombocytopenia during formestane treatment

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Formestane is a new aromatase inhibitor used as second-line endocrine treatment for postmenopausal women with advanced breast cancer. The most frequent side effects are local reactions. Here we report the development of immune thrombocytopenia coinciding with administration of this drug.

Formestane (4-hydroxyandrostenedione) is a new competitive, irreversible, steroidal aromatase inhibitor, 30 to 60 times more potent than aminoglutethimide.[1] Aromatase is the enzyme responsible for the conversion of non-aromatic androgens, particularly androstenedione and testosterone, to aromatic estrogens: estrone and estradiol. In postmenopausal women androstenedione is converted to estrogens by aromatase in the skin, muscles, liver and fat tissue. Aromatase is also present in breast tumor tissue. Thus, formestane decreases both circulating and tumour estrogen levels and is a successful second-line endocrine treatment for post-menopausal women with advanced breast cancer in whom previous therapy with tamoxifen has failed.[1-3]

The most frequent side effects are local and transient reactions at the site of injection (gluteal pain,

erythema, pruritus, burning, abscesses). Mild systemic effects usually include hot flushes, rash, lethargy, dizziness, emotional lability, facial swelling, alopecia, vaginal spotting, nausea, leukopenia, constipation or rarely anaphylaxis.[4-6]

To date, there have been no reported cases of formestane-induced thrombocytopenia. Here we describe a case of transient, severe, immune thrombocytopenia during formestane administration.

A 55-year-old woman was referred to our department for evaluation of severe thrombocytopenia. Four years previously, an infiltrating ductal breast carcinoma ($T_2N_{1b}M_0$) was diagnosed and treated with surgery (radical mastectomy), standard chemotherapy according to the CAF regimen (cyclophosphamide, doxorubicin and 5-fluorouracil) and radiotherapy to scar and nodal areas. Two years after diagnosis, due to skeletal metastases, the patient was placed on endocrine therapy with tamoxifen. Two years later, X-rays and gammagraphy showed progression of metastases (D10-L5), and palliative radiotherapy was planned. Tamoxifen was changed for formestane at 250 mg i.m. every second week. Platelet count was 189×10^9/L.

After 3 doses of formestane a full blood count revealed severe thrombocytopenia: 17×10^9/L. There was no evidence of a hemorrhagic diathesis. Peripheral blood smears showed normal morphology and a *true* thrombocytopenia was confirmed: there were no platelet aggregates. EDTA-dependent pseudothrombocytopenia was ruled out. A bone marrow biopsy showed normocellularity, with an increased number of megakaryocytes. No evidence of tumor infiltration was found. Viral serological studies were negative. Other tests such as detection of antiphospholipid antibodies were also negative. A serologic study of platelet antibodies with the platelet immunofluorescence test[7] revealed the presence of an IgG platelet autoantibody: positive direct test and eluate. Drug dependent antibodies (*immune complexes* and *adsorption* mechanisms) were also investigated according to the methodological procedures described by Mueller-Eckhardt *et al.*[8] The *immune complex* mechanism was investigated incubating formestane with the serum of the patient before adding the target platelets. The *adsorption* mechanism was studied preincubating platelets with the offending drug and washing them before the serum of the patient was added. Neither mechanism seemed to be involved in the platelet destruction. Taking into account the serological results a *drug-independent* mechanism for formestane-induced immune thrombocytopenia was considered.

All treatment was discontinued. Regular follow-up was planned. The platelet count progressively recovered, returning to normal 4 months after the last dose of formestane. A new serologic study of platelet antibodies performed at this time was negative.

Although some drugs may induce thrombocytopenia by impairing megakaryocyte production (i.e. chemotherapeutic agents or thiazide diuretics), most drugs cause thrombocytopenia by eliciting an immune response.[9] Our patient developed severe thrombocytopenia (17×10^9/L) after 3 standard doses of formestane. As she was asymptomatic, formestane was stopped and no further treatment was required. Serological studies revealed the presence of a transient IgG platelet autoantibody. The serological findings, similar to those found in idiopathic autoimmune thrombocytopenia, and the clinical course were consistent with a *drug-independent* mechanism of formestane-induced thrombocytopenia. The list of drugs potentially capable of causing immune thrombocytopenia[10] is continuously growing.

Key words

Formestane, immune thrombocytopenia, side effects, platelet autoantibodies

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