

Propylthiouracil-Related Hemorrhagic Diathesis:

A Case Report and Review of the Literature

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Abstract

We present an unusual case of a drug-related hemorrhagic diathesis. One month prior to admission, the patient was diagnosed at another medical center as having Graves' disease and propylthiouracil therapy (PTU) was initiated. Since clinical recovery was not achieved, the PTU was quickly increased to an unconventional daily dose of 1,000 mg. The patient was referred to our hospital because of spontaneous epistaxis, multiple ecchymoses and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), which developed soon after the increase in PTU dose. Drug-related hemorrhagic diathesis was considered, after other possible causes had been eliminated. To the best of our knowledge, this is the first reported case of spontaneous hemorrhage due to PTU use.

Key Words: Propylthiouracil, hemorrhagic diathesis, factor deficiency.

Case

A 23-YEAR-OLD WOMAN was admitted to our university hospital because of epistaxis and ecchymoses over multiple areas of her skin, especially on her lower extremities. She had been well until one month earlier, when tremor, tachycardia, heat intolerance, irritability and anxiety developed. A diagnosis of Graves' disease had been established at another hospital, and 300 mg of daily PTU (in three divided doses) was begun. As no notable clinical and laboratory improvements were achieved, the PTU dose was increased to an unconventional dose, 1,000 mg daily (in five divided doses). After a few days epistaxis developed, and the patient reported the passage of tarry stools. On physical examination at our hospital, she appeared anxious, was tachycardic (120 beats/minute) but afebrile at 36.4°C, and had blood pressure of 120/80 mm Hg in both arms. Multiple ecchymoses

and petechiae were seen on her abdomen, lower extremities and back. Heart sounds were distant and lungs were clear on auscultation. The extremities and abdomen were normal, except for the ecchymoses. A complete blood count revealed a hemoglobin level of 12.8 g per liter with a mean corpuscular volume (MCV) of 82.4 μm^3 , a white cell count of 8,860 cells/ mm^3 and a platelet count of 505,000 cells/ mm^3 . Serum levels of electrolytes, creatinine, blood urea nitrogen, albumin, total protein, calcium and bilirubin were normal, as were the results of liver-function tests and urinalysis. A chest radiograph and ultrasound of the abdomen were both normal. An electrocardiogram revealed sinus tachycardia at a rate of 120 beats/min with no ischemic findings. The admission PT and aPTT were 195 and 102 seconds, respectively. Bleeding and clotting times were within normal ranges. Drug-related hemorrhagic diathesis was considered as a cause of the abnormal findings.

Discussion

When a bleeding patient presents with substantially prolonged PT and aPTT and normal platelet counts, certain causes should be considered. These causes, as listed in Table 1 (1), were not compatible with this patient's presentation, since levels of fibrinogen, factor VIII and von Willebrand factor (vWF) were normal and the pa-

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TABLE 1
Reasons for Prolongation of Both PT and aPTT with a Normal Platelet Count

| Bleeding | No Bleeding |
|--------------------------------------------------------|------------------------------------------|
| Afibrinogenemia | Hypofibrinogenemia |
| Severe deficiencies of factors II, V and X | Mild deficiencies of factors II, V and X |
| Combined factors V and VIII deficiency | |
| Combined deficiency of the vitamin K-dependent factors | |
| Acquired inhibitors to factors II and V | |
| Acquired factor X deficiency | |

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tient had no history of inappropriate or prolonged bleeding.

A tendency towards bleeding has been reported among patients using thionamide drugs. However, this tendency is rare and has only been observed in patients undergoing surgical interven-

tions. On the other hand, coagulation studies of our patient revealed a very severe deficiency of all vitamin K-dependent factors (Table 2). In the reported cases, decreased levels of prothrombin were thought to be responsible for the bleeding (2, 3). However, no hemorrhagic diathesis has been reported among patients using thionamides in the absence of surgical trauma. In the literature, several cases of bleeding diathesis and thrombocytopenia, attributed to PTU use, have been reported (4). In our case, the thrombocyte count was normal.

PTU-associated vasculitis has been reported in a few cases (5–7). More specifically, well-defined, PTU-induced, small vessel vasculitis and alveolar hemorrhages, which are associated with antineutrophil cytoplasmic antibody (ANCA) development, have been reported (8, 9). However, by history, on physical examination and according to the laboratory data, our patient had no features consistent with vasculitis.

As mentioned above, our patient had no history of bleeding and her family history was unremarkable. She had not used any drugs prior to her intake of PTU. She had had a normal PT and aPTT on routine testing prior to treatment at the previous

TABLE 2
Hematological Laboratory Values

| Variable | Admission | Day 1 | Day 2 | Day 6 | On Discharge (Day 12) |
|----------------------------------------|--------------------|-------|-------|---------------------|-----------------------|
| Hematocrit (%) | 36 | | | | 35 |
| WBC (cells/mm ³) | 8,680 | | | | 7,680 |
| Platelet (cells/mm ³) | 505,000 | | | | 393,000 |
| Thyroid functions* (TSH, T3, T4) | (0.11; 5.17; 3.43) | | | (0.027; 4.32; 2.08) | |
| D-dimer (µg/dL)# | 0.22 | | | 0.22 | |
| Fibrinogen (mg/dL)¶ | 408 | | | 484 | |
| ANA (anti-nuclear Ab) | Negative | | | | |
| P-ANCA | Negative | | | | |
| C-ANCA | Negative | | | | |
| Antiphospholipid ab. IgG | Negative | | | | |
| Antiphospholipid ab. IgM | Negative | | | | |
| Bleeding time (Ivy) (min) ^f | 4.2 | | | | |
| vWF [‡] | 160 | | | | |
| AT III (%)≠ | 112 | | | | |
| Prothrombin | 1 | | | | 83 |
| Factor VII (%) | 15 | | | | 90 |
| Factor VIII (%) | 113 | | | | 110 |
| Factor IX (%) | 10 | | | | 80 |
| Factor X (%) | 17 | | | | 95 |
| PT (sec) ^f | 195 | 46.5 | 41.4 | 39.2 | 18 |
| aPTT (sec) ^f | 102 | 69.4 | 54.4 | 56 | 36 |
| CRP (mg/dL) | 12.4 | | | | |

CRP = C-reactive protein, WBC = white blood cells, AT = antithrombin, C-ANCA=cytoplasmic antineutrophil cytoplasmic antibody, P-ANCA = perinuclear antineutrophil cytoplasmic antibodies.

Normal ranges: *TSH (0.27–4.2), fT4 (0.93–1.7), fT3 (1.8–4.6); #D-dimer (0–0.4); ¶Fibrinogen (200–400); ^fBleeding time (3–6); [‡]vWF (50–160); ≠AT III (80–120), Factor II-VII-VIII-IX-X (60–150); ^fPT (11–14.2), aPTT (26–37.2).

medical center and during a routine laboratory examination performed one year earlier. When we stopped the PTU and administered vitamin K, the patient's levels of prothrombin and of factors VII, IX and X normalized within 12 days (Table 2). In view of this, we concluded that high-dose PTU had caused an inhibition of vitamin K and, consequently, of vitamin-K-dependent coagulation factors. Subsequently, she was treated with a 200 mg daily dose of methimazole, while monitored closely. Fortunately, no further complications occurred.

One might argue that the elevation in factor levels was due to administration of fresh frozen plasma. However, we only infused four units of fresh frozen plasma (FFP) on admission, along with one dose of vitamin K after evaluating the patient. Four units of FFP would not be expected to cause such a dramatic increase in factor levels. During a follow-up visit one month after discharge, and while the patient was still on 200 mg of methimazole daily, all her factor levels were still in the normal range.

One question of great interest is whether the hemorrhagic diathesis we observed is a dose-dependent effect. In our patient, no hemorrhagic diathesis had occurred while she was receiving 300 mg of PTU prior to admission, or while she was on methimazole following discharge. Thionamide drugs (propylthiouracil and methimazole) resemble the methyltetrazole-thiol leaving group of certain cephalosporin antibiotics, and both thionamides and cephalosporins have been found to inhibit the vitamin-K-dependent gamma-carboxylation of glutamic acid *in vitro* (2). Probably, mild clotting factor deficiencies due to inhibition of this step occur in many patients, though this remains subclinical at regular doses. The important point here is that higher doses of thionamide drugs might cause hemorrhagic diathesis, especially in patients taking oral anticoagulants and in patients who already have a tendency to bleed due to idiopathic thrombocytopenic purpura or other predisposing conditions.

Conclusions

This presented case is unusual and warrants reporting for several reasons. First, to the best of our knowledge, spontaneous hemorrhage while on PTU, in the absence of trauma or surgical interventions, has not been reported previously in the literature. Second, although thrombocytopenia associated with PTU usage has been reported, no clotting factor deficiencies have been reported until now. Moreover, deficiency of vitamin-K-dependent coagulation factors due to PTU use has only been demonstrated in cats, not in humans. Hence, to our knowledge, this is the first case of a human patient on high-dose PTU exhibiting vitamin-K-dependent factor deficiency.

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