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Acquired von Willebrand's Disease, IgE Polyclonal Gammopathy and Griseofulvin Therapy

To the Editor: Acquired von Willebrand's disease (AVWD) by definition occurs in individuals without a bleeding history or family history of von Willebrand's disease (VWD). In most instances, AVWD has been related to another disease process. The associated disease processes include myeloproliferative syndromes [1], autoimmune disorders [2], malignant B cell disorders and monoclonal gammopathy of uncertain significance [3], hypothyroidism [4], Wilms' tumor [5], congenital cardiac disease [6], angiodysplasia [7], and Ehler-Danlos syndrome [8]. It has also been reported following the prolonged use of hydroxyethyl starch [9]. A patient is reported without evidence of one of these disease processes. He had been on griseofulvin for a skin dermatitis for 2 months (330 mg/day). The AVWD abated with cessation of griseofulvin therapy. This is the first report, to our knowledge, of AVWD's occurring in association with antibiotic therapy.

A 51-year-old black male developed painful swelling in his right calf. An abnormal bleeding time (>20 min) and partial thromboplastin time (65 sec) were found. Following the venipuncture, he developed painful swelling in the right biceps region. He was transferred to University Hospital with the above findings and several areas of ecchymosis. There was no family history of a bleeding disorder. The patient had six dental extractions during the prior 20 years without significant bleeding. His three children were tested and showed normal bleeding times, partial thromboplastin times, and factor VIII assays. Physical examination was unremarkable except for the findings described previously. There was no adenopathy, hepatosplenomegaly, or thyromegaly. The white blood count was 14,200 cells/mm^3 with 75% neutrophils, 19% lymphocytes, and 6% monocytes. Hemoglobin was 9.5 g/dl with a mean corpuscular volume of 90 fl. Platelet count was 361,000 cells/mm^3. Blood chemistries were normal. Coagulation studies showed a prothrombin time 11 sec, partial thromboplastin time 59 sec, fibrinogen 465 μg/dl, bleeding time >20 min, factor $VIII_A$ 12%, factor $VIII_C$ 10% and von Willebrand's factor antigen activity 8%. There was no inhibitor. Serum protein electrophoresis showed no monoclonal protein spike. Immunoglobulins showed an IgE 1,714 units/ml (N=10–180 μ/ml). IgG 2261 mg/dl (N=570–1,480 mg/dl) with a normal IgA (407 mg/dl) and IgM (108 mg/dl). Serum iron was 20 μg/dl, total iron binding capacity was 280 μg/dl. Thyroid studies were normal. ANA was non-reactive. Serologic tests for syphilis and HIV were non-reactive. A bone marrow biopsy and aspirate showed a normocellular marrow with increased storage iron. Bone films for myeloma and computerized axial tomography of the chest, abdomen and pelvis for adenopathy were non revealing. Griseofulvin therapy was stopped on admission. The patient was treated with cryoprecipitate every 12 hr for 5 days and this corrected his coagulation abnormalities. His coagulation tests remained normal after cessation of cryoprecipitate and were normal one month and three months after discharge. His IgE was 450 units/ml and IgG was 1,935 mg/dl. He has had no evidence of bleeding or ecchymoses.

A patient with AVWD is described who developed coagulation abnormalities and bleeding into skin and muscles while receiving griseofulvin. He had a markedly elevated IgE and mildly elevated IgG. There was no history of allergies. A relationship between the griseofulvin, abnormal immunoglobulins and AVWD is speculative. However, recovery was prompt and durable with cessation of drug therapy.

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Cytarabine and Cardiac Failure

To the Editor: Congestive heart failure has been reported in patients receiving cytarabine but was attributed to other drugs, including anthracyclines and alkylating agents, administered with it [1,2]. Acute respiratory distress with pulmonary edema and cardiomegaly was reported after high dose cytarabine [3]; a direct cardiotoxic effect was thought to be unlikely because patients had a normal capillary wedge measurement while in pulmonary edema. A Japanese patient was reported who developed congestive heart failure following high dose cytarabine therapy [4]. However, that patient received previous treatment for acute leukemia with doxorubicin and cyclophosphamide.

A young patient with chronic granulocytic leukemia is reported who developed congestive heart failure on two occasions following treatment with cytarabine as a single agent.

A white female sought medical attention for fatigue in September 1981 at age 21 years. She had a white blood count of 123,000 cells/mm^3; platelets 617,000 cells/mm^3 and a hemoglobin 10.7 g/dl. A bone marrow biopsy specimen was hyperplastic and shown to contain Ph′ chromosome positive cells. She had no HLA compatible siblings. She was treated periodically with hydroxyurea for control of splenomegaly, leucocytosis, and thrombocytosis until 1989. On August 7, 1989, she was seen with multiple tender subcutaneous masses which were slightly movable and surrounded by a halo of ecchymosis (pseudochloromas) [5]. Her spleen was enlarged to the iliac crest. White blood count was 290,000 cells/mm^3 with many myelocytes and metamyelocytes but no blasts in the peripheral smear. Hemoglobin concentration was 11.5 g/dl and platelet count was 587,000 cells/mm^3. Partial thromboplastin time was 34 seconds and prothrombin time was 12.4 seconds with a bleeding time of 20 minutes. Platelet aggregation studies were normal. While receiving oral allopurinol, the patient was given 5 g of cytarabine intravenously every 12 hours for a total of four doses to treat the extramedullary leukemic infiltrates and avert progression to the central nervous system [5]. The spleen rapidly decreased in size and the subcutaneous masses resolved. Serial serum chemistries showed no evidence of the tumor lysis syndrome. On August 14, 1989, the white blood count was 4,300 cells/mm^3 with 66 segmenters, 26 lymphocytes, 2 monocytes, and 6 basophils. Hemoglobin concentration was 8.6 g/dl and platelet count was