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LETTERS AND CORRESPONDENCE

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Treatment of Thrombotic Thrombocytopenic Purpura With Defibrotid

To the Editor: Thrombotic thrombocytopenic purpura (TTP) is a disease with rapid onset, dramatic clinical presentations, and a high mortality rate. Although current treatment regimes lower mortality, there is no current consensus on the type of treatment [1]. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, central nervous system abnormalities, and renal dysfunction. Some of the criteria of TTP may develop late [1] or may not occur [2].

Diseases such as disseminated intravascular coagulation, carcinoma, eclampsia, hemangiomas, toxins, and radiation-induced intravascular red cell fragmentation (microangiopathic hemolysis) should be distinguished from TTP, and patients with thrombocytopenia and microangiopathic hemolytic anemia with no identifiable cause can be considered as having mild TTP. Although there are several hypotheses to explain the increased platelet aggregation and adhesion and endothelial cell damage observed in TTP, the cause and pathogenesis remain unknown [3].

Defibrotid is a single-stranded polydeoxyribonucleotide obtained from DNA of mammalian lungs by controlled depolymerization. It has a modifying effect on impaired endothelial cell function and increases tissue plasminogen activator (t-PA) and prostacyclin (PGI_2) production while decreasing plasminogen activator inhibitor (PAI) levels. Defibrotid has an inhibitory effect on platelet function, while strong antithrombotic effects have been demonstrated in animal experiments [4]. It effectively inhibits platelet aggregate formation in the microarterial anastomosis in rats and also increases the reendothelization of anastomotic line [5]. In the light of this known effect on endothelial cells and platelets, this drug has been used in deep vein thrombosis (DVT), peripheric occlusive vein disease (POVD), and stroke, with encouraging results [4]. We have administered this drug to a 39-year-old female with TTP, with good results.

Case Report

E.Y., a 39-year-old female, was completely well until the sudden onset of fatigue, generalized petechiae and purpura in May, 1991. There was no history of drug ingestion, toxin exposure or recent infection. Examination revealed a normal blood pressure, pallor, and generalized petechiae and purpura. There was neither hepatosplenomegaly nor lymphadenopathy. The patients joints were completely normal, and no edema was present. Hemoglobin concentration was 7.1 g/dl, platelets were 11,600/mm^3, reticulocytes were 14.2%. There was severe red blood cell fragmentation and a marked decrease of platelets in the blood smear. Direct Coombs, indirect Coombs, ANA, and anti-DNA tests were negative. Granular and hyaline cast were visible in the urine sediment. There was erythroid hyperplasia and an increase in megakaryocytes in the bone marrow aspirate.

Megadose methylprednisolone (30 mg/kg/day) was administered as a 1 hr IV infusion for 3 days with no response. Defibrotid (600 mg twice daily) was administered as an IV infusion over 1 hr for 15 days as an alternative therapy. There were no side effects. The patient's petechiae began to resolve reticulocytes fell to 4.5%, platelets increased to 580,000/mm^3, and the peripheral blood smear showed an improvement in RBC structure and morphologically normal platelets after 2 days. The patient received the drug for 15 days with no side effects. She has remained healthy during the subsequent 13 months follow-up period.

Discussion

There is an increased platelet aggregation and adhesion in TTP. Several platelet-aggregating substances have been reported as the cause of disease, i.e., several small proteins [6], calpain (a calcium activated cysteine protease) [7], and large and "unusually large" von Willebrand (vWF) multimers [8]. Endothelial cell injury or intense stimulation of endothelial cells results in the secretion of unusually large vWF multimers. Severe episodes of TTP are best reversed by plasma exchange (the combination of plasmapheresis and normal fresh-frozen platelet-poor plasma infusion) [1]. Plasma infusion alone may be sufficient in some patients. Some patients who are resistant to plasma exchange therapy may respond to infusion of cryosupernatant fraction of plasma [9]. Chemotherapy with vincristine in combination with plasmapheresis has also been found effective [10]. Corticosteroids either alone or in conjunction with azathioprine have been used, with some benefit in a few patients [2]. A few patients have been reported to benefit from splenectomy [2]. Although we were unable to assay unusually large vWF multimer in our patient, defibrotid may instigate its effect by reducing endothelial cell derived unusually large vWF multimers.

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Iatrogenic Osteomalacia Caused by Intravenous Administration of Saccharated Ferric Oxide

To the Editor: Saccharated ferric oxide (SFO; trade name Fesin) is most frequently used as the intravenous iron preparation. We have experienced a case of osteomalacia caused by the long-term administration of SFO. Seven cases of osteomalacia [1–4] caused by SFO have been reported. These patients were not suitable for the long-term administration of SFO. They may thus be called cases of iatrogenic osteomalacia.

A 58-year-old woman was admitted to our hospital because of progressive osteodynia in October, 1990. According to her history, she was found to have mild anemia (Hb 10.8 g/dl) in August, 1989 and was commenced on SFO by a local doctor. About 4 months after starting SFO administration, ankle and knee pain appeared. The pain progressively worsened and back pain, chest pain, and hip pain were added. On admission, no distinctive findings were noted except knocking pain of the sternum, ribs, and lumbar vertebrae. Laboratory tests showed mild normochromic anemia (Hb 10.5 g/dl). The alkaline phosphatase (ALP) was high (977 IU/liter) and the serum phosphate level as low (1.4 mg/dl). Serum iron was high (168 μg/dl), and ferritin was abnormally high (4,050 ng/dl). The parathyroid hormone was normal. TRP was low at 72.5%. Technetium-99 bone scintigraphy showed abnormal uptake around the shoulders, ribs, hips, and ankles. After admission, the SFO, which had been administered for about 1 year, was withdrawn, and milk was given to improve her hypophosphatemia. The phosphate level increased to a normal range in 3 weeks. Bone pain, ferritin, and ALP levels also gradually improved.

Since the first report [1], eight cases including our case have been reported of osteomalacia caused by SFO (Table I). There were five patients with iron deficiency anemia (may be misdiagnosis). In all of these patients, bone pain appeared 3–4 months after starting the administration of SFO, and dysbasia was observed. The bone pain improved after withdrawal of SFO in all cases. Hypophosphatemia, abnormal uptake of phosphate in the renal tubules, and high ferritin and ALP levels were commonly observed. Also, improvement of these abnormalities after withdrawal of SFO was also observed. Although bone biopsy was not performed in our case, it was performed in three of the eight patients and a definite diagnosis of osteomalacia was made. Okada et al. [5] reported that when SFO was administered for 14–42 days to nine patients with anemia, hypophosphatemia developed in all cases. The mechanism of hypophosphatemia caused by SFO is not clear. However, osteomalacia due to SFO may be caused by hypophosphatemia.

Thalassemic osteoarthropathy caused by iron deposition has been reported. These cases, however, differ from osteomalacia caused by SFO in their clinical features. When other iron preparations are administered orally or intravenously, neither hypophosphatemia nor osteomalacia has been reported. Consequently, it is considered that osteomalacia is specifically associated wit SFO. Osteomalacia caused by the long-term administration of SFO has been reported only in Japan. This perhaps depends on the misuse and overuse of intravenous iron preparation in Japan.

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TABLE I. Cases of Osteomalacia Caused by Saccharated Ferric Oxide

Patient	Age (years)	Sex	Underlying disease	Dose (mg/day)	Ca (mg/dl)	P (mg/dl)	Repot
1	46	Female	Intestinal ulcer	80	8.9	1.0	Okada et al., 1982
2	37	Female	Intestinal ulcer	40	9.5	1.0	
3	58	Female	Anemia	80	9.6	2.0	Sasaki et al., 1987
4	55	Female	Malabsorption	Unknown	8.2	1.6	Kuranobu et al., 1990
5	61	Female	Anemia	Unknown	8.1	1.9	
6	51	Female	Anemia	Unknown	7.4	1.9	
7	47	Female	Anemia	40	8.0	1.5	Mizumoto et al., 1990
8	58	Female	Anemia	40	9.4	1.4	Our case, 1993