

CASE REPORTS

Case report of a patient with Klinefelter syndrome treated with testosterone injections presenting with thrombotic thrombocytopenic purpura

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Abstract

Thrombotic thrombocytopenic purpura (TTP) has been described as a pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurologic signs, renal impairment and fever. Guidelines for treating patients with Klinefelter syndrome (KS), the most common chromosome aneuploidy, include testosterone replacement. We present the first case of adult with KS who presented with TTP after treatment with intramuscular testosterone injection. Whether or not the presentation is an association or coincidence is unknown, though in this report, we summarize the current understanding of testosterone supplementation in patients with KS. Original articles, case reports and reviews were obtained using a MEDLINE search between 1948 and 2013. Retrospective studies have concluded that in patients with KS there was an increased incidence of hematologic malignancies with erythrocytosis being the only consistently documented hematologic abnormality associated with testosterone supplementation. A randomized, placebo-controlled study is needed to access the long-term effects of testosterone treatment in patients with KS.

Keywords

Klinefelter syndrome, Thrombotic thrombocytopenic purpura, Testosterone

1 Introduction

Thrombotic thrombocytopenic purpura (TTP), first described in 1925, as a pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurologic signs, renal impairment and fever is a rare and potentially lethal disease with a mortality of 90% if left untreated. Klinefelter syndrome (KS) is the most common chromosomal aneuploidy and is characterized by hypergonadotropic hypogonadism. Guidelines for treating patients with KS include testosterone replacement. We present the first case of adult with a diagnosis of KS who presented with TTP after treatment with testosterone injections.

2 Case

A 51-year-old man with a medical history of hypertension, type 2 diabetes mellitus and Klinefelter syndrome treated with intramuscular testosterone injections for 3 months prior to admission, presented to our emergency department following a motor vehicle accident. Upon arrival temperature was 38.4°C. The patient had altered mental status and subsequently was intubated for airway protection. Initial lab results included white blood cell count 12,000/ul with 14% bands, hemoglobin 8.4 mg/dl (MCV 85.7 fL) and platelet count of 5,000/ul (MPV 7.5 fL). Direct Coombs was negative, lactate dehydrogenase 1247 u/L and the reticulocyte count was 6.1%. Additional labs included a blood-urea nitrogen 25 mg/dl, creatinine 1.1 mg/dl, total bilirubin 2.2 mg/dl, direct bilirubin 0.4 mg/dl and lactic acid 3.0 mEq/L. Coagulation studies were negative as was HIV ELISA. Peripheral blood smear revealed schistocytes confirming the diagnosis of TTP. Daily plasma exchange was begun, and after five days of this treatment platelet count had reached 156,000/ul. The patient confirmed that he had no exposure to quinine and the only new medication he had received was the testosterone injections. ADAMTS13 (A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13) activity level returned at 32% (Blood Center of Wisconsin; < 67% abnormal, < 5% severe deficiency) with anti-ADAMTS13 antibody of 13 (Blood Center of Wisconsin; < 18 negative, 19-27 indeterminate, > 28 positive). Following an extensive hospital course our patient was discharged home, clinically improved on a tapering dose of prednisone.

3 Discussion

TTP, first described in 1925, is reported to have an annual incidence of 4 to 11 cases per million people with a mortality of 90% if left untreated ^[1, 2]. The syndrome, initially classified as a pentad of thrombocytopenia, MAHA, fluctuating neurologic signs, renal impairment and fever was later revised to include anyone with thrombocytopenia and MAHA ^[3]. Pathogenesis includes a deficiency of ADAMTS13, a von Willebrand Factor (vWF) cleaving metalloprotease protein ^[4, 5]. Measurement of pre-treatment ADAMTS13 and ADAMTS13 IgG antibody is helpful to confirm the diagnosis, although due to the high mortality, treatment should be initiated within 4-8 hours of high clinical suspicion of TTP ^[1, 6]. It is important to note that cohort studies have shown the sensitivity of the ADAMTS13 testing ranges from 33 to 100 percent, and that patients with TTP may have normal levels ^[7]. TTP has been classified into congenital and acquired, the latter being associated with pregnancy, HIV, organ transplant, pancreatitis, malignancy, drug-induced and most commonly, idiopathic ^[8]. Drugs documented to induce TTP include quinine, mitomycin-C, cyclosporine, clopidogrel and ticlopidine ^[9]. Oral contraceptive pills and estrogen hormone replacement therapy are known to provoke thromboembolic events and have been suggested to have an association with TTP ^[10, 11]. Westerlund *et al.* investigated this correlation by measuring clotting factors throughout an in-vitro fertilization (IVF) cycle. As estradiol levels increased so did levels of Factor VIII, vWF activity and antigen; levels of ADAMTS13 activity and antigen decreased ^[12]. The primary hematologic side effect of testosterone supplementation documented is erythrocytosis, with guidelines advising hematocrit testing initially every three months followed by annual surveillance ^[13-15]. Thrombocytopenia has not been associated with testosterone supplementation.

KS, first described in 1942 has an estimated incidence of 1 per 500 births with a prevalence of 150 per 100,000 live-born males ^[15]. It is the most common chromosome aneuploidy, is characterized by hypergonadotropic hypogonadism and is confirmed by karyotype analysis ^[15, 16]. Pathogenesis involves non-disjunction during germ or early embryonic cell divisions and thus has numerous chromosomal aberrations, the most common being 47, XXY ^[16]. KS is widely under-diagnosed, and has been associated with increased mortality both overall and from secondary associated medical conditions ^[15]. These conditions include motor, cognitive and behavior dysfunction, osteoporosis, metabolic syndrome and diabetes mellitus ^[15]. There is a higher risk of developing certain malignancies including mediastinal cancers in children ^[17] and breast cancer and non-Hodgkin's lymphoma in adults ^[18]. Regarding hematologic associations, retrospective studies and literature reviews have concluded that KS was more likely "discovered" in hematologic malignancies and thus larger studies are needed ^[19, 20].

Testosterone, the first line agent treatment of KS has been associated with erythrocytosis, prostate enlargement, and reduced fertility [14]. Clinical guidelines advise against treatment of men with metastatic prostate cancer, breast cancer, unevaluated prostate nodule, prostate-specific antigen greater 4 ng/ml, hematocrit greater than 50% and poorly controlled heart failure [15]. Randomized, placebo controlled studies of long term testosterone supplementation in KS patients have not been published, though literature has described improved sexual function and mood, increase in lean body mass with a decrease in fat mass [21]. Interestingly one study in 2000 published by Kocar *et al.* observed that in Klinefelter patients treated with testosterone immunologic parameters including immunoglobulins and interleukins decreased after treatment [22]. Erythrocytosis is the only consistently documented hematologic abnormality that has been associated with testosterone supplements [13-15]. We are reporting the first adult case of patient with Klinefelter syndrome (XXY) treated with testosterone injections who presented with thrombotic thrombocytopenic purpura. Of note there is one reported case report documenting a 13-year-old XYY child who died from TTP, however there is no mention of testosterone use [23].

4 Conclusion

In summary we present a 51-year-old man with recent diagnosis of KS who was undergoing treatment with testosterone injections and presented with TTP. Whether the testosterone injections were the culprit remains unknown, however re-challenging him with testosterone supplementation poses too much of a risk. Interestingly, studies in women who have received testosterone have shown that although testosterone effects endothelial marker proteins including vWF, these effects do not change the endothelial cell functioning [24, 25]. A randomized, placebo-controlled study is needed to assess the long-term effects of testosterone treatment in Klinefelter patients. Until then a correlation, if any between Klinefelter patients treated with testosterone and TTP remains unknown. With the increase in number of patients with KS receiving testosterone supplementation hopefully we will be able to determine if a causal relationship exists.

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