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OBSTETRICS & GYNECOLOGY | CASE REPORT

Type I plasminogen deficiency with unexpected clinical aspects: Could be more than coexistence?

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Abstract: Type I plasminogen deficiency is a rare autosomal recessive systemic disorder. It usually starts in infancy and is clinically characterized by chronic mucosal pseudomembranous lesions which contain largely fibrin due to diminished extracellular plasmin mediated fibrinolysis. The most common clinical manifestation occurs in conjunctiva and therefore the disease is also named as ligneous conjunctivitis. Though type I plasminogen deficiency is known to cause female infertility due to genital tract inflammation and destruction, no male infertile patient with ligneous conjunctivitis was reported to date. In this case report, two siblings, both had ligneous conjunctivitis and gingivitis are presented. The male patient had primary infertility and his sister who was also infertile had neuroendocrine carcinoma. Both of the patients were found to be homozygous for *PLG* gene IVS6 + 1 G > A (c.668 + 1G > A) mutation. Plasmin and fibrinolysis pathway play important role in male infertility and our patient's infertility could be due to type I plasminogen deficiency.

Subjects: Medical Genetics; Obstetrics, Gynecology & Women's Health; Urology

Keywords: ligneous conjunctivitis; plasminogen deficiency; *PLG*; infertility

1. Introduction

Type I plasminogen deficiency is an autosomal recessive disorder. It was first described in 1847 and first detailed histological description was reported in 1924 (Schuster & Seregard, 2003). In 1997, Schuster et al. demonstrated plasminogen (*PLG*) gene mutations for the cause of the disease

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PUBLIC INTEREST STATEMENT

Type I plasminogen deficiency is a rare autosomal recessive systemic disorder. Though type I plasminogen deficiency is known to cause female infertility due to genital tract inflammation and destruction, no male infertile patient with ligneous conjunctivitis was reported to date. Plasmin and fibrinolysis pathway may play an important role in male infertility. Deficient plasminogen activity could cause ligneous inflammation in male genital tract, reduce liquefaction of semen, affect sperm maturation and capacitation. To our knowledge, this is the first male infertile patient with type I plasminogen deficiency in the literature. Similar cases in this subject will further help to definite relationship between male infertility and the disease.

This case would provide new information to the literature and we believe that the case would be interesting for genetic counseling issues.

(Schuster & Seregard, 2003; Schuster et al., 1997). Plasminogen gene is located on 6q26-27. Impaired secretion of mutant plasminogen proteins is the general molecular pathology in the disease (Schuster & Seregard, 2003; Tefs et al., 2006). The estimated prevalence of the disease is 1.6/1,000,000. In countries like Turkey where consanguineous marriage is more frequent, the prevalence may be higher.

The most common clinical manifestation is in conjunctiva with pedunculated pseudomembranous lesion; hence the disease is also named as ligneous conjunctivitis. Additionally, involvement of gingiva, buccal mucosa, nasal mucosa, middle ear, larynx, trachea bronchial tree, kidney and female genital tract could be seen and a limited number of children with ligneous conjunctivitis has been reported to suffer from congenital occlusive hydrocephalus and juvenile colloid milium (Chowdhury, Blackford, & Williams, 2000; Schuster & Seregard, 2003). Although lots of treatment modalities was attempted, no sufficient treatment is achieved in this disease (Schuster & Seregard, 2003).

2. Clinical summary

In 1990, a 15 year old male patient, first child of a consanguineous couple, was consulted to our department for short stature and pubertal delay. His medical history revealed that he suffered from bilateral conjunctival plaques since infancy and he had some gingival problems starting from 14 years of age. The plaques could be seen in his detailed physical examination. His G-band karyotype was normal. The family also mentioned that their daughter had similar plaques in her eyes and gingiva. In 2008, he was consulted again to our department from urology clinic due to infertility. In his sperm analysis azospermia was detected. His peripheral blood FSH level was 7,24 mIU/mL whereas LH level was 4,52 mIU/mL and total testosterone level was 443,7 ng/dL (normal values: FSH:7.63–42.6 mIU/mL, LH:1.5–12.4 mIU/mL, total testosterone:280–800 ng/dL). On his physical examination several teeth lost were detected and his conjunctival plaques were still visible. High resolution karyotype analysis was normal and SRY, AZFa, AZFb and AZFc regions were detected to be normal in microdeletion analysis. From the pedigree analysis, it was found out that his sister suffering from mucosal plaques was also infertile.

Homozygous *PLN* gene IVS6 + 1 G > A (c.668 + 1G > A) mutation was identified in the siblings. As the father was dead, only the mother's DNA could be obtained. Their mother was found to be heterozygous for the same mutation.

3. Discussion

There are two types of plasminogen deficiency: Type I is characterized by decreased plasminogen activity, plasminogen antigen levels and clinical symptoms. Type II (dysplasminogenemia) is characterized by decreased plasminogen activity with normal or slightly reduced antigen levels. Type I plasminogen deficiency is a very rare autosomal recessive disease caused by plasminogen gene (*PLG*) mutations. Impaired secretion of mutant plasminogen proteins is the general molecular pathology of the disease. Plasminogen is converted to active plasmin in circulation and plasmin, as a fibrinolytic enzyme, degrades fibrin in wound healing process. Hence, in patients with plasminogen deficiency, impaired wound healing causes the formation of fibrin rich pseudomembranes due to the lack of proteolytic activity (Mehta & Shapiro, 2008; Schuster & Seregard, 2003; Tefs et al., 2006).

Most cases of ligneous conjunctivitis are sporadic and female/male ratios range from 1.4:1 to 2:1. This is confusing because in an autosomal recessive disease female/male ratio is expected to be 1:1. It may be due to additional predisposing factors such as hormones.

Siblings presented here suffered from ligneous conjunctivitis since infancy and gingivitis since teenagers. Female patient had severe ligneous conjunctivitis. She had undergone several ophthalmologic surgeries because of large conjunctival pseudomembranes which unfortunately regrew rapidly.

Though we did not test PLG antigen levels and PLG activity, plasminogen gene mutation analysis confirmed that our patients have type I plasminogen deficiency. During the preparation of this manuscript, IVS6 + 1 G > A mutation was reported by Dönmez Demir in two individual Turkish patients. This mutation alters splicing and causes PLG deficiency (Dönmez-Demir et al., 2016).

Both of our patients were also infertile. Ligneous female genital tract inflammation have been reported in several patients with or without ocular involvement and can cause dyspareunia, dysmenorrhea, vaginal discharge and primary infertility (Altinkaya, Uzunlar, Talas, Ozat, & Bilge, 2008; Schuster & Seregard, 2003). Schuster et al. mentioned that fertility is generally decreased in a woman with ligneous vulvovaginitis and/or conjunctivitis (Schuster & Seregard, 2003). Histopathological, chronic inflammatory changes, which contain amorphous eosinophilic, amyloid-like subepithelial fibrin deposits are detected. Amorphous deposits include fibrillary material. Besides, ligneous inflammation is recurrent and in chronic manner and this is thought to be the reason of female infertility (Altinkaya et al., 2008). These data were supported by numerous mice models. Ploplis et al. showed that plasminogen-deficient female mice suffered from reduced fertility (Ploplis et al., 1995). Lund et al. showed that mammary gland development and involution and fertility compromised in primiparous plasminogen-deficient (Plg(-/-)) female mice (Lund et al., 2000). On the other hand, though extensive uterine involvement, a case who delivered two healthy full term infants was reported (Chi et al., 2009).

To our knowledge, no male infertile patient with type I plasminogen deficiency has been reported up to date. Our male patient suffered from primary infertility. He had azospermia with normal FSH, LH and testosterone levels. Plasminogen, plasminogen activator inhibitor (PAI-1), tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) were all described in human semen. Plasmin plays an important role in the liquefaction of human semen (Lwaleed, Goyal, Delves, & Cooper, 2007). Van Dreden et al. showed that PAI was absent or at the detection limit in normospermia, besides PAI antigen and activity levels were high in oligoastenoteratospermia or azospermia (Van Dreden, Audrey, & Aurélie, 2007). In a case control study Ebisch et al. found that t-PA concentrations were higher in spermatozoa of the male factor subfertility group compared to fertile and idiopathic subfertile men. Moreover, they demonstrated that t-PA concentration in spermatozoa was notably associated with pregnancy (Ebisch et al., 2007). In a review of Ebisch et al. the role of PA system in male was explained as spermatocytes transition of blood testis barrier, epidymal maturation of spermatozoa, sperm surface capacitation modifications, acrosome reaction, zona pellucida attachment and facilitation of spermatozoa to move into the tubes (Ebisch et al., 2008). With all the above proofs, plasmin and fibrinolysis pathway may play an important role in male infertility. Deficient plasminogen activity could cause ligneous inflammation in male genital tract, reduce liquefaction of semen, affect sperm maturation and capacitation. Unfortunately, we were unable to analyze plasminogen antigen level, plasminogen activity, PAI-1, t-PA, u-PA levels in our patient's semen. Relationship between male patient's infertility and plasminogen deficiency is needed to be proven.

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Competing Interests

The authors declare no competing interest

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