Ligneous Cervicovaginitis

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Ligneous inflammation is a rare systemic disorder which can affect the conjunctiva, the female genital tract, the upper and lower respiratory system, the gingiva, and the ears [1–3]. The ocular mucosa is the most common site involved. It can be diagnosed by the examination of biopsy material histopathologically. In histopathologic examination, chronic inflammatory changes, which contain amorphous, eosinophilic, amyloid-like subepithelial fibrin deposits, are encountered. Amorphous deposits include fibrillar material consistent with fibrin [4]. These eosinophilic fibrin deposits are periodic acid–Schiff (PAS)-positive material accompanied by inflammatory cellular infiltration.

Ligneous inflammation is a recurrent, chronic inflammatory disorder for which curative treatment is not available. Most gynecologists are unfamiliar with this diagnosis, and lack of awareness of this unusual entity can cause diagnostic difficulties [4].

Autosomal recessive inheritance is said to be responsible for the disorder, and there are also familial cases [5]. Recently, plasminogen deficiency has been found to be responsible for ligneous changes because of an inability to remove fibrin which is deposited in injured mucosal tissue [6,7].

A 22-year-old married woman presented at our gynecology clinic with dyspareunia and dysmenorrhea. She had also been suffering from primary infertility for two years. She complained about a white vaginal discharge which included white plaques, and her symptoms worsened prior to her menses.

On gynecologic examination, the cervix was found to be deformed and there were hard white plaques, which showed inflammatory reactions, at the vaginal fornixes and around the cervix (Figures 1 and 2). In the medical investigation of infertility, her basal hormones (follicle-stimulating hormone, luteinizing hormone, estradiol, thyroid-stimulating hormone, prolactin levels on the third day of the menstrual cycle) were normal.

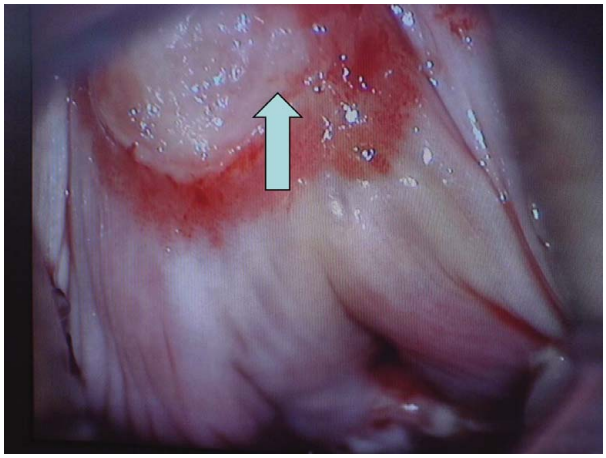

Figure 1. Ligneous plaques (arrow) around the cervix.

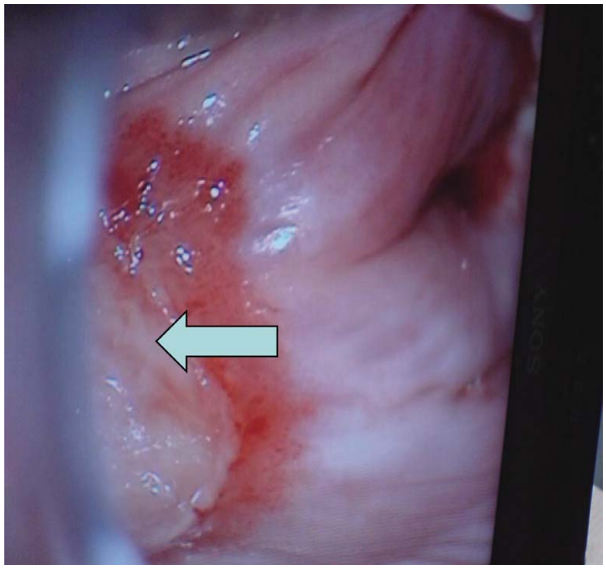

Figure 2. Ligneous plaques (arrow) at the lateral fornix.

Her husband's spermiogram was normal, and hysterosalpingography revealed patent tubes and adequate uterine cavity. Transvaginal ultrasonography was conducted, and the uterus, ovaries and endometrium were found to be normal. Because of her vaginal discharge, cervicovaginal culture, fresh examination and smear staining were conducted. There was no evidence of *Candida* and *Trichomonas*, and no clue cell was observed. The whiff test and *Chlamydia* antigen test were negative, and

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Gram-negative diplococci like *Neisseria gonorrhoeae* were not observed. In the serologic tests, *Chlamydia* IgG and IgM, herpes simplex virus 2 IgG and IgM were negative. VDRL, rapid plasma reagin and *Treponema pallidum* hemagglutination tests were conducted for sexually transmitted diseases like syphilis and were found to be negative. The complete blood cell count, liver, kidney and thyroid function tests, and blood glucose level were found to have normal values. Additional tests were conducted, including prothrombin time (12.3 seconds; reference, 11–15 seconds), fibrinogen (326 mg/dL; reference, 144–430 mg/dL), D-dimer (0.38 mg/mL; reference, 0.00–0.50 mg/mL), activated partial thromboplastin time (32.5 seconds; reference, 25–40 seconds). In her lipid profile screen, total cholesterol was 165 mg/dL (reference, < 200 mg/dL), HDL cholesterol was 42 mg/dL (reference, 35–65 mg/dL), LDL cholesterol was 105 mg/dL (reference, < 150 mg/dL) and lipoprotein(a) was 8 mg/dL (reference, 0–30 mg/dL). A hypercoagulability screen was conducted; antithrombin III activity was 106% (reference, 80–120%), protein C activity was 109% (reference, 70–130%), protein S activity was 130% (reference, 60–140%), activated protein C resistance was 183 seconds (reference, 120–300 seconds), factor XII was 103% (reference, 60–140%). Plasminogen functional activity was 50% of normal (reference, 55–145%), tissue plasminogen activity (tPA) was 4 ng/mL (reference, 1–12 ng/mL), and plasminogen activator inhibitor 1 (PAI-1) was higher than normal at 4.2 U/mL (reference, 0.3–3.5 U/mL).

Histopathologically, samples of cervix and vagina showed a fibrinous material surrounding the cervical glands in the subepithelial area, disintegrated keratinized cells, and infiltrations of lymphocytes and polymorphonuclear leucocytes. Acantholytic changes and dyskeratotic cell groups were determined in the metaplastic squamous epithelium. There was subepithelial deposition of a dense, amorphous, eosinophilic material associated with intense inflammatory cell infiltration. The deposits showed positive staining for PAS and phosphotungstic acid-hematoxylin (Figures 3 and 4). Staining reactions showed that the amorphous material contained fibrin.

The histopathology was consistent with ligneous inflammation. Considering that the most frequent site involved is the ocular mucosa, an ophthalmologic examination was held and no evidence of ligneous inflammation was found. Autosomal recessive inheritance is said to be responsible for the disorder, so chromosomal analysis was made and a 46,XX karyotype was found. From the patient's medical history, her mother and father were determined to be cousins. There was no familial history of inflammatory eye disease and neither

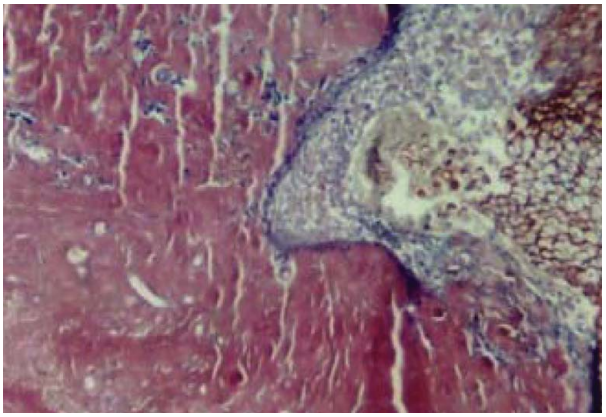

Figure 3. Positive staining for periodic acid–Schiff.

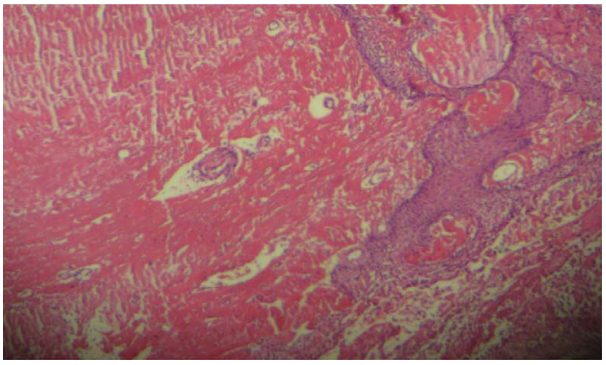

Figure 4. Amorphous, eosinophilic material in the subepithelial area.

of her sisters suffered from ligneous inflammation of the female genital tract, eye or any other sites.

Ligneous inflammation is a rare systemic disorder which can affect the conjunctiva, the female genital tract, the upper and lower respiratory system, the gingiva, and the ears [1–3]. As the ocular mucosa is the most common site of involvement, it has almost completely been in the province of ophthalmology. The number of cases which have ophthalmologic involvement is much greater than those having female genital tract involvement. Up to the present, 18 cases on ligneous inflammation involving the female genital tract have been published in English (Table). The cervix and vagina appear to be the main genital sites of affliction. There is no information or data on ligneous inflammation in most gynecology textbooks. Ligneous inflammation may cause infertility because of its effects on endometrial, tubal, tubo-ovarian or even cervical function [3].

Ligneous inflammation was first mentioned in the literature as conjunctivitis in 1953 [16]. Bateman et al mentioned ligneous inflammation as an autosomal recessive genetic disorder in 1986 [5]. In 1997, Mingers et al reported homozygous type 1 plasminogen deficiency in ligneous inflammation of the conjunctiva and extraocular pseudomembranous lesions [17]. In 1999, Schuster

Table. Eighteen cases published in English on ligneous inflammation involving the female genital tract

References	Number of patients reported	Clinical characteristics	Laboratory findings
Lotan et al [8]	1	Extensive involvement of female genital tract, ear	Functional plasminogen activity was 13% of normal
Karaer et al [9]	1	Involvement of female genital tract, oral mucosa, conjunctiva	Functional plasminogen activity was 18% of normal
McCullough et al [10]	1	Involvement of female genital tract, conjunctiva, ear, gingiva	Functional plasminogen activity was 12% of normal
Deen et al [11]	1	Involvement of female genital tract, no ocular or respiratory symptoms	Functional plasminogen activity was 36% of normal
Tefs et al [12]	4	Report of 50 patients, four of whom had female genital tract involvement	NA
Kayikcioglu et al [2]	1	Involvement of female genital tract and conjunctiva	Functional plasminogen activity was 16% of normal
Pantanowitz et al [7]	1	Involvement of female genital tract, middle ear, oral mucosa	Functional plasminogen activity was 12% of normal
Chakravarti et al [13]	1	Involvement of female genital tract and conjunctiva	NA
Pantanowitz et al [4]	1	Involvement of female genital tract, conjunctiva, ear, gingiva	NA
Scurry et al [3]	2	Two women, both of them had genital tract involvement and no ocular disease	NA
Ridley and Morgan [14]	1	Involvement of female genital tract and conjunctiva	NA
Rubin et al [15]	1	Involvement of female genital tract, conjunctiva, gingiva	NA
Hidayat et al [1]	2	Report of 17 patients, two of whom had female genital tract involvement	NA
Total	18		

NA = not available.

et al described compound heterozygous missense mutations in the plasminogen gene in the development of ligneous conjunctivitis [18]. In 2004, type 1 homozygous plasminogen deficiency was reported in a patient who had genital tract, middle ear and gingiva involvement by Pantanowitz et al [7].

Ligneous changes are believed to appear owing to plasminogen deficiency which results in inability to remove fibrin mostly in mucosal sites secondary to previous injury or inflammation, resulting in increased accumulation of fibrin deposits. In ligneous lesions, a preponderance of fibrin determines whether ligneous lesions may arise because of defective fibrin degradation. Ramsby et al [19] described impaired fibrin degradation at both cellular and biochemical levels. Impaired fibrin degradation can result from a variety of defects which affect plasmin generation or activity, including deficiency of plasminogen or t-PA, excess of PAI or plasmin activator inhibitor, or lipoprotein(a) or abnormalities in matrix structure, function or interaction. Although our patient's tPA level was within normal limits, the PAI-1 level was higher and plasminogen was lower than normal.

Relative plasminogen deficiency which results in hypofibrinolysis is known to arise following inhibition of plasmin binding to fibrin and secondary to increased plasminogen degradation. Binding of plasmin to fibrin is inhibited by lipoprotein(a) [19]. Increased values of lipoprotein(a) interfere with plasmin-mediated fibrinolysis [20]. Our patient had a normal lipoprotein(a) level.

Heparin, steroids, hyaluronidase, cyclosporin and α-chymotrypsin have been attempted in treatment, but none of them have been consistently effective. Treatment of ligneous conjunctivitis with topical plasmin was not effective, while topical plasminogen had a good effect [21]. In another study, two patients with ligneous conjunctivitis and plasminogen deficiency were treated with oral contraceptives, and an increment in plasminogen was gained. Oral contraceptives inhibited the progression of ligneous changes in one of these patients and

abolished the ligneous changes completely in the other [22]. Oral contraceptive treatment is worth considering in selected cases of plasminogen deficiency.

Acknowledgments

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