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Case study

Inherited plasminogen deficiency presenting as ligneous vaginitis: a case report with molecular correlation and review of the literature

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Summary Type 1 plasminogen deficiency is an inherited and potentially life-threatening systemic disease in which patients develop pseudomembranous lesions of mucosal surfaces exposed to minor trauma. It is most commonly clinically encountered as ligneous conjunctivitis. We report the case of a 39-year-old woman with extensive involvement of the female genital tract. Microscopically, the vagina, cervix, endometrium, ovaries, and parametrial tissues showed innumerable deposits of paucicellular hyaline material with adjacent inflammation. Histochemical, immunofluorescent, and electron microscopic analyses revealed the amorphous material to be fibrin and collagen. In the plasma, functional plasminogen and plasminogen antigen levels were markedly decreased. Sequencing showed the patient to be a compound heterozygote for a missense and nonsense mutation in the plasminogen gene. Histologically, deposits in ligneous vaginitis are easily confused with amyloid or fibrinous debris. Recently, replacement therapy with plasminogen has been shown to significantly improve systemic symptoms, making ligneous mucositis a serious but treatable condition.

1. Introduction

Ligneous conjunctivitis is a rare disease in which patients develop pseudomembranous, "woodlike" lesions of mucosal surfaces. Although it was named for the dramatic lesions of the conjunctiva that typically arise during childhood, ligneous conjunctivitis is truly a systemic condition. In addition to ocular lesions, many patients develop pseudomembranous involvement of other mucosal surfaces exposed to repetitive trauma, including the mouth, nasopharynx, tracheobronchial tree, intestines, and the female genital tract. Patients often present with conjunctival membranes as young children, and some progress to have corneal involvement and may become blind, whereas others experience spontaneous regression of pseudomembranes [1]. With time, patients may develop gingival hyperplasia and hoarseness [2]. Occasionally, life-threatening respiratory distress or intestinal obstruction may be caused by the pseudomembranes [1].

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In humans, as well as in mouse models, it has recently become clear that ligneous conjunctivitis is caused by type 1 plasminogen deficiency, a form of inherited hypoplasminogenemia that is characterized by low levels of active and immunoreactive plasminogen [1,3]. Type 1 plasminogen deficiency has been linked to a variety of homozygous or compound heterozygous mutations of the plasminogen gene, of which the K19E missense mutation is the most common (comprising 34% of mutations in a recent series) [3]. These mutations most likely result in rapid degradation of plasminogen, a key component of the fibrinolytic system [3]. The formation and subsequent resorption of a temporary fibrin matrix is a critical event during wound healing; thus, a decrease in active plasminogen levels leads to the accumulation of fibrin at sites of repetitive mucosal trauma. These fibrin deposits may form a small subepithelial mass, leading to further mucosal ulceration and initiating a vicious cycle of tissue damage and fibrin deposition. Here, we present a case of a patient with inherited hypoplasminogenemia and extensive ligneous involvement of the female genital tract, with laboratory and molecular correlation.

2. Case report

A 39-year-old G_0P_0 woman was referred for surgical management of a previously diagnosed clear cell carcinoma of the vagina. Her gynecologic history was significant for multiple abnormal Papanicolaou test results, as well as vaginal strictures necessitating surgical intervention at age 20. In addition, she had a 7-year history of primary infertility and had undergone hysteroscopy and laparoscopy 6 months before her presentation. The operative findings at that time included a constrictive ring in the upper vagina at the cervicovaginal junction. In addition, extensive pelvic adhesions involving the uterus and the left ovary were noted, without gross or histologic evidence of endometriosis. Biopsies obtained directly from the vaginal stricture showed architecturally complex and cytologically atypical glands haphazardly distributed in a hyalinized stroma (Fig. 1A and B). These were interpreted as being consistent with invasive clear cell carcinoma by pathologists from 2 independent institutions (including our department). Significantly, there was no history of diethylstilbestrol exposure.

At our hospital, repeat vaginal examination showed no evidence of residual stricture with focally denuded mucosa at the cervicovaginal junction consistent with a prior biopsy site. To identify the extent of disease, she underwent additional biopsies distal to this prior biopsy site, which showed only tuboendometrial-type vaginal adenosis in an extensively hyalinized stroma. Based on these findings, a radical hysterectomy with bilateral salpingo-oophorectomy, upper vaginectomy, and paraaortic lymph node sampling was performed.

2.1. Pathologic features

Gross examination of the vaginectomy specimen revealed a focally gray and roughened vaginal mucosa devoid of stricture or masses. The vaginectomy specimen, cervix, ovaries, and fallopian tubes were completely submitted for histologic examination. Final pathologic examination revealed extensive tuboendometrial-type vaginal adenosis with focal cytologic atypia but lacking the architectural complexity present in the original biopsy specimen (Fig. 2A and B). There was no evidence of tumor in any of the paraaortic lymph nodes; thus, based on the vaginal involvement in the original biopsies, the patient remained at FIGO stage I (pT1 NO MX). Postoperatively, the patient had poor wound healing and developed multiple polypoid nodules of the vaginal cuff. In conjunction with Papanicolaou tests showing atypical glandular cells, she underwent a series of vaginal biopsies over a period of 6 months to assess for recurrent clear cell carcinoma.

All of the postoperative vaginal biopsies showed extensive hyaline deposits with fibrinous debris overlying an ulcerated mucosa (Fig. 1C and D). Retrospective review of the original vaginectomy and radical hysterectomy/bilateral salpingo-oophorectomy specimens revealed similar histologic findings (Fig. 2). Beneath the vaginal mucosa, there were extensive deposits of paucicellular, amorphous, eosinophilic material with an adjacent chronic inflammatory infiltrate containing lymphocytes, plasma cells, and occasional neutrophils. In some areas, the eosinophilic material was fibrinous, whereas in other areas it appeared more organized with collagen deposition. Focally, this hyaline-like material formed a membrane overlying the ulcerated surface. Similar deposits were present within the fallopian tube fimbriae and parametrial tissues, as well as in the endometrium and cervical mucosa. In the ovary, deposits of hyalinized material were present in place of normal corpora albicantia. Congo red staining for amyloid was consistently negative. Immunohistochemistry for CD61 highlighted aggregates of platelets within the deposits, and results of immunofluorescent studies for fibrinogen were strongly positive (Fig. 3). Electron microscopy confirmed that the amorphous material consisted of fibrin admixed with occasional collagen fibrils.

2.2. Laboratory results

Additional history obtained from the patient after a series of biopsies revealed that she had chronic periodontal problems, “granulomas” of the ear, and intermittent hoarseness for many years. There was no clear history of ocular disease. Based on her clinical history and histologic findings, plasma was obtained from the patient to measure functional plasminogen and plasminogen antigen levels. Functional plasminogen level was markedly decreased at 13% of normal (reference range, 70%-127%), and plasminogen antigen