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How I treat type 1 plasminogen deficiency

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Abstract:
Type 1 plasminogen deficiency (PLGD), an ultra-rare disorder caused by PLG pathogenic variants, results in decreased levels of immunoreactive and functional plasminogen. PLGD can cause fibrin-rich pseudomembranes on mucosa that impair tissue/organ function, impact quality of life, and are potentially life-threatening. Lesion regression/resolution is facilitated by intravenous administration of human plasma-derived Glu-plasminogen (IV PLG concentrate), the first and only FDA-approved specific treatment, licensed in 2021. The diagnosis of PLGD is frequently delayed due to its rarity (1.6 per million) and the variability of the initial medical specialty contact determined by the affected systems. Symptoms are often attributed to more common conditions, like conjunctivitis, recurrent otitis media, reactive airway disease, etc. This manuscript presents clinical vignettes highlighting strategies for PLGD diagnosis and treatment. Initial evaluation includes a detailed history, laboratory assays, and, at times, radiologic or other procedures. Genetic testing can confirm the diagnosis. Consistent, knowledgeable management is required to promptly identify and treat lesions, even in initially asymptomatic individuals. Personalized treatment may include continuous prophylaxis or intermittent treatment with IV PLG concentrate, dependent on disease severity and clinical course. Specialized facilities like Hemophilia Treatment Centers offering multidisciplinary care represent medical homes for this ultra-rare disorder.

Conflict of interest: COI declared - see note

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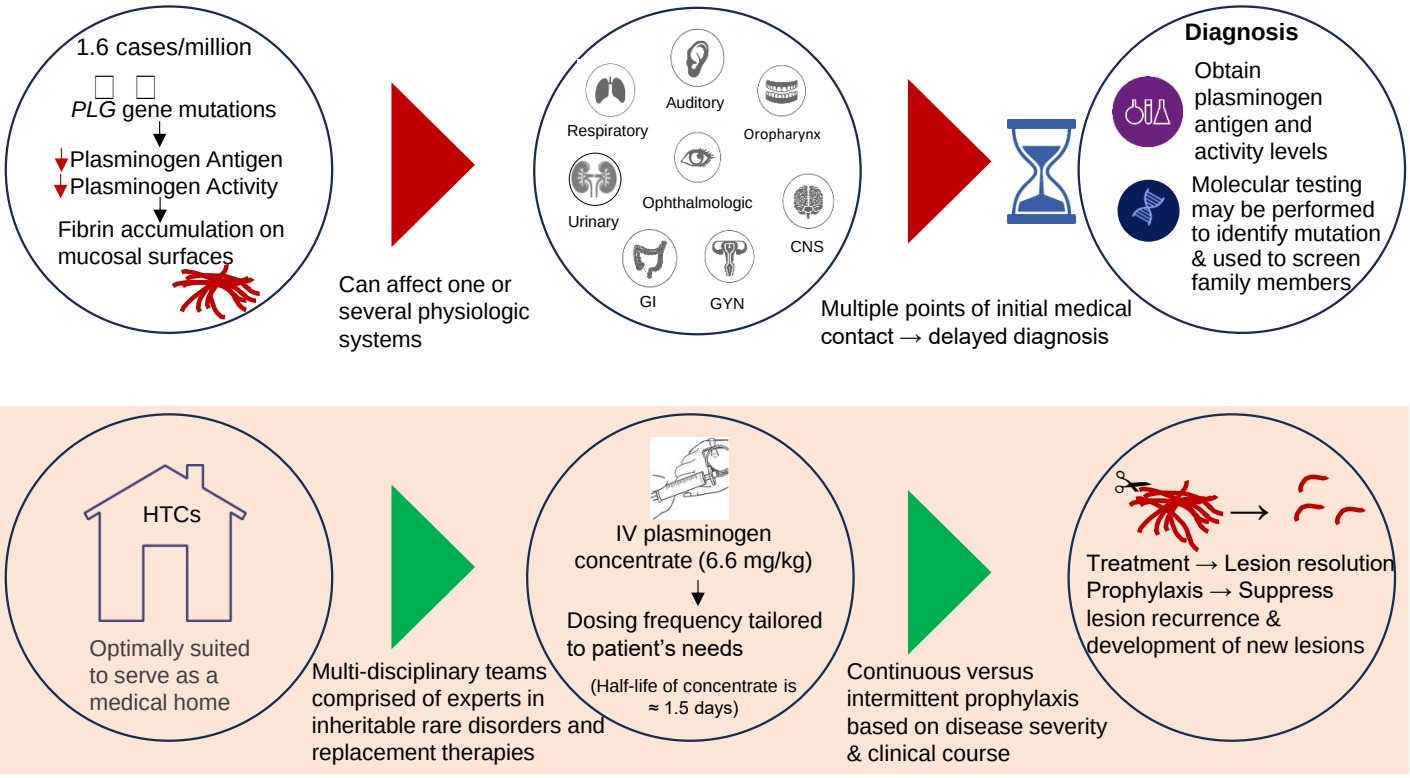
How I Treat Type 1 Plasminogen Deficiency (PLGD)



Conclusions: PLGD diagnosis is frequently delayed due to its rarity and variability of the initial medical specialty contact; symptoms are often attributed to more common conditions. Effective treatment was demonstrated with the FDA-approved targeted therapy, IV plasminogen concentrate. Optimal outcomes require consistent, knowledgeable management; facilities such as HTCs encompass the needed expertise and services to provide comprehensive, coordinated care.

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blood Visual Abstract

How I treat type 1 plasminogen deficiency

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Abstract

Type 1 plasminogen deficiency (PLGD), an ultrarare disorder caused by *PLG* pathogenic variants, results in decreased levels of immunoreactive and functional plasminogen. PLGD can cause fibrin-rich pseudomembranes on mucosa that impair tissue/organ function, impact quality of life, and are potentially life-threatening. Lesion regression/resolution is facilitated by intravenous administration of human plasma-derived Glu-plasminogen (IV PLG concentrate), the first and only FDA-approved specific treatment, licensed in 2021. The diagnosis of PLGD is frequently delayed due to its rarity (1.6 per million) and the variability of the initial medical specialty contact determined by the affected systems. Symptoms are often attributed to more common conditions, like conjunctivitis, recurrent otitis media, reactive airway disease, etc. This manuscript presents clinical vignettes highlighting strategies for PLGD diagnosis and treatment. Initial evaluation includes a detailed history, laboratory assays, and, at times, radiologic or other procedures. Genetic testing can confirm the diagnosis. Consistent, knowledgeable management is required to promptly identify and treat lesions, even in initially asymptomatic individuals. Personalized treatment may include continuous prophylaxis or intermittent treatment with IV PLG concentrate, dependent on disease severity and clinical course. Specialized facilities like hemophilia treatment centers offering multidisciplinary care represent medical homes for this ultrarare disorder.

Introduction

Type 1 plasminogen deficiency (PLGD), or hypoplasminogenemia, is an autosomal recessive disorder affecting 1.6 individuals per million. PLGD is characterized by decreased plasminogen antigen and activity levels[1] caused by homozygous or compound-heterozygous mutations in the *PLG* gene.[2,3] The association between plasminogen deficiency and its most common manifestation, ligneous conjunctivitis (LC), was established in 1997[4,5] (Figure 1). Plasminogen is produced primarily in the liver and smaller amounts in the cornea[6], kidneys, adrenal glands, brain, testes, intestines, genital tract, and vascular linings.[6-9]

Plasminogen exists in two main forms: Glu- and Lys-plasminogen. Glu-plasminogen contains a glutamic acid at its N terminus and has a half-life of 2.2 days.[10] Lys-plasminogen has a lysine residue at the N terminus, a half-life of 0.8 days, possesses a more open conformation, and circulates at significantly lower concentrations.[11,12] Plasmin converts Glu-plasminogen into Lys-plasminogen, increasing its sensitivity to activation by plasminogen activators and creating a positive feedback loop.[13]

Plasminogen activation by tissue-type plasminogen activator (tPA) and urokinase plasminogen activator (uPA) converts plasminogen to the serine protease plasmin.[14-16] Fibrin is a strong promoter of plasminogen activation, facilitating the binding of plasminogen and plasminogen activator to its surface, thereby enabling rapid cleavage of plasminogen into plasmin.[13] Plasminogen is a key regulator of fibrinolysis, and its other

functions that may contribute to disease expression include complement inhibition,[17] extracellular matrix degradation,[18] cell migration,[19] and inflammation resolution.[20]

PLGD is primarily associated with the formation of fibrin-rich membranes on mucosa, particularly affecting the eyes, followed by the respiratory tract, oropharynx/gingiva, auditory system, central nervous system, genitourinary tract, and gastrointestinal tract.[1,3,21-25] Case reports of poor wound healing in people with PLGD support the role of plasminogen in wound healing.[26] The expression of PLGD symptoms is highly variable; some patients experience continuous symptoms, others experience fluctuations, and some remain asymptomatic for many years. This variability poses significant challenges in differential diagnosis and management.[3,22,24,25,27,28] PLGD is characterized by impaired maintenance of the extracellular matrix and fibrinolysis rather than intravascular thrombosis.[29] Indeed, several population-based studies found no correlation between PLGD and increased risk of thrombosis.[30-33]

Historically, no therapeutic intervention consistently prevented or resolved disease manifestations (supplemental Table 1). In 2021, the U.S. FDA approved Ryplazim (plasminogen, human-tvmh), a plasma-derived human Glu-plasminogen (IV PLG concentrate), the first and currently only approved PLGD-specific systemic treatment. IV PLG concentrate raises plasminogen levels, which decline with a half-life of 34 to 39 hours,[34] and has been to resolve and/or prevent disease manifestations.[35,36]

The multisystemic nature of PLGD, gaps in understanding disease triggers, variable expressivity, and the absence of defined severity categories pose challenges in differential diagnosis and management.[3,22,24,25,27,28] Current treatment decisions, including use of intermittent therapy based on lesion presence or surgical interventions or longer-term disease suppressive regimens such as prophylaxis with an identified target trough level, are often individualized based on disease burden and patient history.

Diagnosis

PLGD diagnosis is based upon clinical suspicion due to characteristic lesions such as LC, followed by laboratory confirmation of plasminogen activity/antigen (PLG-act/ag) levels (Figure 2). Genetic testing for pathogenic *PLG* variants can support diagnosis and be used for screening asymptomatic family members. A comprehensive review of systems (ROS) is required to determine all areas of past or current involvement.[3,5,37]

The relationship between PLG-act/ag levels or *PLG* variants and disease severity is unclear. Notably, patients with more severe clinical presentations do not uniformly have the lowest PLG-act/ag levels; however, patients with levels ≤10% typically present at a younger age and with more persistent symptoms.[38]

Initial assessment

Patients with PLGD should be referred to a hematologist, optimally part of a hemophilia treatment center (HTC), where expertise in coagulation protein deficiencies, their multisystem manifestations, along with replacement therapy is available. The hematologist can determine the need for further sub-specialist evaluation (e.g., ophthalmologists, dentists, otolaryngologists) and coordinate care to optimize outcomes, [39,1,5,24,27,28,37,38,40-43,44,45] [24,46] including replacement therapy for invasive procedures. A gynecological ROS is required for affected females regardless of age; if symptoms are identified, a gynecologic evaluation is recommended based on the patient's age and comfort level. Patients with a history of suspected reactive airway disease should undergo a thorough physical examination and assessment of respiratory status (respiratory rate, work of breathing, oxygen saturation, pulmonary function testing, or radiologic evaluation).[22,47] Invasive procedures must be co-managed by an HTC to ensure safety. This comprehensive multidisciplinary approach facilitates the identification, evaluation, and long-term management of multisystem manifestations (Figure 3).

Dosing frequency and duration

The treatment cornerstone for symptomatic PLGD is plasminogen replacement with IV PLG concentrate, which has demonstrated safety and efficacy in resolving and preventing disease manifestations. [35,36,48,49] The approved treatment regimen is 6.6 mg/kg every 2 to 4

days to achieve a targeted trough level of 10% above baseline PLG-act. Regular assessment of symptoms and PLG-act inform ongoing treatment decisions (Table 1).

In cases of respiratory involvement (e.g., dyspnea, hypoxemia, or hypercapnia), especially in young children, therapy is initiated in a monitored setting with daily treatments until stabilized, after which infusion intervals are gradually extended (i.e., daily to every other day to every 3 days). Dose intervals may be adjusted based upon venous access, symptoms, and lesion control to establish a stable prophylactic regimen. In children, limited venous access may necessitate the placement of central venous access devices for continuous therapy; in the absence of long-term therapy, these devices tend to form fibrin sheaths and become dysfunctional.

Cases

The following clinical vignettes highlight disease manifestations, treatment approaches, and current knowledge gaps in PLGD management (Table 2).

Case 1: Ligneous conjunctivitis

A 14-year-old adolescent boy (PLG-act <2%) was diagnosed at the age of 7 years. His history includes recurrent left LC (Figure 4) unresponsive to topical steroids and antibiotics that began at diagnosis. After undergoing 3 left lower eyelid membrane strippings with rapid lesion recurrence, he began treatment with fresh frozen plasma (FFP) eye drops every 2 hours while awake for 2 years, with clinical benefit despite adherence challenges. When

locally produced FFP eye drops became unavailable, the left eye lesions worsened, and he developed chronic right eye conjunctivitis without membranes; treatment included topical corticosteroid, immunosuppressant containing cyclosporine, and antihistamine. Transient intraocular pressure elevations occurred with topical steroids. At age 10, recurrent otitis media developed, leading to adenoidectomy and bilateral myringotomy with tympanostomy tube placements requiring replacement after dislodgement into the middle ear. Following the second set of tubes and adenoidectomy, there were no further ear infections or hearing impairment. On evaluation at age 14, the lower left eyelid lesion remained without associated pain or visual changes.

LC occurs in approximately 80% of symptomatic individuals. The median age of presentation is 10 months, with symptoms reported as early as the first weeks of life.[3,4,42] Despite <2% PLG-act, this patient developed LC in one eye at age 7. This case highlights the knowledge gap in understanding the correlation between plasminogen levels and clinical symptomatology. Injuries, infections, or ocular surgeries may trigger lesions. Initial symptoms include chronic tearing, conjunctival erythema, and photophobia, with progression to pseudomembrane development primarily on the palpebral surfaces. Eventually, pseudomembranes transform into thick, woody white, yellow, or red lesions that disrupt and replace normal mucosa. LC commonly recurs or worsens after excision without adequate replacement therapy. Initially, LC can resemble bacterial conjunctivitis, pyogenic granuloma, conjunctival papilloma, or inclusion cyst; inclusion of PLGD in the differential diagnosis is essential.

Treatment with IV PLG concentrate commenced thrice weekly for 2 weeks, followed by twice weekly for 8 weeks, with significant improvement in LC. After 10 weeks, minimal residual lesions remained, and infusion frequency was reduced to once weekly, with all lesions resolved. Treatment was discontinued 1 month after full resolution with close monitoring for symptom recurrence.

Ligneous conjunctivitis in PLGD

IV PLG concentrate therapy can lead to rapid LC improvement. Long-standing lesions may require prolonged treatment, with residual fibrous areas requiring surgical removal under the cover of replacement therapy. Without replacement therapy, lesion removal leads to rapid regrowth and increased risk of corneal abrasions, visual impairment, amblyopia, and vision loss. Coordinating ophthalmologic care with an HTC is crucial for optimal outcomes. LC can occur at any age and may remit and recur over many years. Individuals with LC as their only presentation can be effectively treated with IV PLG concentrate; once resolved, infusion frequency may be reduced under close observation.

Case 2: Respiratory lesions

A 37-year-old woman, initially diagnosed with PLGD at the age of 14 years (PLG-act<5%), presented with multisystem involvement, including life-limiting respiratory complications (chronic cough interrupting sleep, posttussive emesis, chronic bronchodilator use, inability to exercise, and impaired quality of life [QOL]). Her 1-second forced expiratory volume

(FEV-1) was 46.7% of normal (1.57 L). A chest radiograph revealed persistent right upper lobe atelectasis secondary to bronchial obstruction. Bronchoscopy identified 3 ligneous lesions in the bronchial tree. Otoscopic examination revealed a nasal lesion and a small LC on the right upper eyelid; extensive gingival lesions were observed.

This patient exhibited LC beginning at age 2, underwent multiple surgical membrane removals, and was treated with topical therapies, including corticosteroids, antihistamines, heparin, cyclosporine, and FFP eye drops. A renal parenchymal lesion was detected at age 8. At age 15, she developed persistent tracheobronchial lesions, resulting in dyspnea, hypoxemia, and upper airway obstruction, necessitating multiple invasive procedures for lesion removal from the trachea, bronchus, and nasal passages. Recurrent right upper lobe collapse and severe bronchiectasis resulted (Figure 5). Extensive periodontal disease characterized by gingival loss and root/nerve exposure required multiple scaling and root planning procedures. Later in life, chronic gastric ulcers and vaginal lesions developed. At age 36, a hysterosalpingogram revealed a blocked fallopian tube and a uterine lesion.

The patient began IV PLG concentrate therapy at 6.6 mg/kg every 2 days, subsequently extended to every 3-4 days. Within hours of the first treatment, the patient reported eased effort and improved breathing depth, along with the expectoration of a large mucus plug. Hematuria initially developed due to renal lesions but cleared thereafter. The patient's eye and gingival lesions resolved after 4 weeks of treatment; at week 12, her nasal lesion resolved, and chest CT demonstrated decreased bronchial lesions, with persistent chronic

right upper lobe atelectasis. Previously identified bilateral renal parenchyma hyperechoic lesions were not detected on follow-up retroperitoneal ultrasound. The chronic cough and posttussive emesis resolved, allowing her to sleep through the night and exercise, and she reported improved QOL.

Respiratory manifestations in PLGD

Respiratory tract lesions occur in 20-30% of PLGD patients and may compromise and/or obstruct airways, resulting in chronic lung disease, bronchiectasis, and, in severe cases, respiratory arrest. Symptoms include cough, dysphonia, aphonia, stridor, wheezing, dyspnea, labored breathing, and hypoxemia.[2,3] Early recognition and prompt treatment are essential to prevent respiratory compromise or failure. For PLGD patients with significant respiratory compromise where there is a potential for life-threatening airway obstruction, admission to an intensive care unit should be considered during and for a period after therapy initiation. This is most common in young children with small airways, where lesion sloughing can result in hemoptysis, hypoxia, and life-threatening airway obstruction. Management should prioritize early treatment. Direct bronchoscopy, along with IV PLG concentrate treatment, should be considered in cases with a significant risk of respiratory obstruction due to age, lesion burden, size, or position to mitigate complications.

Case 3: Management of family members

A 4-year-old healthy girl was diagnosed with PLGD (PLG-act 10%/PLG-ag 4 mg/dL) secondary to her brother's diagnosis at 7 months due to LC. She had three prior episodes

of otitis media and a history of virus-triggered mild reactive airway disease that resolved without sequelae.

At age 5, gingival lesions were identified when molars erupted. (Figure 6 shows an example of gingival lesions in an adult patient.) Lesions were managed conservatively with improved dental hygiene and resolved after the molar eruption completed. She remained asymptomatic until age 9, when she developed vaginal discharge (suspected yeast infection) that resolved after fluconazole treatment, followed by vulvar lesions consistent with external genital ligneous disease.

Families and PLGD

PLGD, an autosomal recessive disease, presents with a 25% chance of each full sibling being affected. Genetic counseling should be offered to all affected individuals and their families. Preemptive testing of at-risk family members should be conducted to ensure regular monitoring of asymptomatic patients and early treatment if required.

IV PLG was initiated at 6.6 mg/kg once weekly with lesion resolution after 2 infusions. Weekly infusions were continued for 1 month and then extended to biweekly without lesion recurrence.

Case 4: Gastrointestinal disease

A 16-year-old adolescent girl, initially diagnosed with PLGD at 8 years of age (PLG-act 17%) following LC presentation since early childhood, necessitating several surgical procedures,

developed gastrointestinal symptoms including tenesmus, frequent rectal mucus discharge, and occasional bright red blood in the stool. Her history included recurrent otitis media during early childhood, requiring myringotomy and tympanostomy tube placements. At age 9, she presented with ligneous vaginitis characterized by intermittent greenish vaginal discharge.

Following diagnosis at age 8, she was treated with IV FFP for ~3 years and FFP eye drops with resultant LC remission. Vaginal lesions were resected at age 10. One episode of transfusion-related acute lung injury and hypertension following IV FFP infusions at age 11 occurred, and therapy was discontinued. After approximately three years without symptoms, she presented with LC at age 14 while weaning off maintenance FFP eye drops administered three times daily. Daily IV FFP was resumed via a peripherally inserted central catheter line, then reduced to once weekly. IV FFP infusions were discontinued after several months due to an allergic reaction. FFP eye drop frequency was increased to 4 times daily with resolution of LC.

Concurrent gastrointestinal and genitourinary symptoms developed, with daily vaginal discharge worsening over 6 months. Vaginoscopy revealed vaginal stricture with white inflamed mucosa and debris. Subsequently, esophagogastroduodenoscopy and colonoscopies with biopsy under FFP infusion coverage were performed. A 15-cm ulcer near the rectum showed fibrin deposits within an inflammatory lesion, consistent with ligneous proctitis rather than inflammatory bowel disease (IBD).

Gastrointestinal manifestations of PLGD

Gastrointestinal tract lesions with potential esophageal, intestinal, and stomach involvement are reported in ~3% of PLGD patients. Gastrointestinal manifestations may include ligneous growths on gastrointestinal mucosa with resultant ulcers. The incidence and severity of gastrointestinal symptoms vary greatly among affected individuals, and prevalence is difficult to establish due to disease rarity, absence of systematic data collection, underreporting or misdiagnosis, and lack of complete evaluations.

Plasminogen infusions were initiated every 3 days, followed by 5-aminosalicylic acid (5-ASA). A follow-up colonoscopy ~1 year later was normal, and 5-ASA was discontinued. IV PLG concentrate infusion was continued every 3 days for ~2 years, with subsequent interval extension to every 4 days. Approximately 6 months after 5-ASA discontinuation and ~1.5 months after IV PLG concentrate infusion interval extension, the patient experienced increased cramping, abdominal pain, and hematochezia (frequency approximately 50%). Repeat colonoscopy with biopsy was consistent with IBD, and 5- ASA was restarted. The infusion interval was reduced to every 2 days with a maintenance regimen of every 3 days initiated upon symptom control 1.5 months later.

IBD has been reported in a limited number of PLGD patients with a causal relationship not definitively established.[50] PLGD may hinder inflammatory lesion healing. In these rare cases, dual therapy for both PLGD and IBD is required.

Case 5: Female organ disease and pregnancy[39]

A 33-year-old woman was diagnosed with PLGD at the age of 6 years (PLG-act 11%). Medical history included LC beginning before the age of 1 year, necessitating 20 surgical removals with rapid recurrence. During adolescence, she experienced dysmenorrhea accompanied by uterine ligneous lesions. At age 27, a hysteroscopy/laparoscopy revealed fibrosis and web-like fibrin-rich adhesions in the uterus and fallopian tubes. At age 28, FFP infusions were initiated, improving ocular symptoms and dysmenorrhea. Vaginoscopy and hysteroscopy performed at ages 29 and 30 identified persistent uterine and cervical fibrin membranes and fallopian tube obstruction with resultant infertility.

This patient exhibited chronic extensive symptomatology, including genital tract lesions with resultant infertility, only partially respondent to IV FFP. At age 33, IV PLG concentrate was initiated in a clinical trial at 6.6 mg/kg every 2 to 4 days. At therapy start, LC and regular but abnormal menses characterized by small amounts of thick, mucus-like discharge lasting 1 to 2 days were present. By week 12 of treatment, LC resolved. After the first menstrual cycle on therapy, she expelled a large mucuslike plug, followed by normal menstruation.

Fertility and PLGD

Approximately 8% of females with PLGD develop genitourinary lesions, specifically ligneous lesions in the female genital tract[3] resulting in abnormal menstrual cycles,

dysmenorrhea, dyspareunia, and infertility. Reported symptoms do not consistently reflect the extent of involvement, and additional evaluations may be required.

The patient reported being pregnant approximately 20 weeks into treatment. After consultation with the clinical study sponsor, regulatory bodies, and the regional ethics committee, continued IV PLG concentrate therapy was approved throughout pregnancy, labor, delivery, and postpartum. The patient experienced an uncomplicated pregnancy and delivered a healthy infant by vaginal birth. Postpartum treatment was continued, maintaining PLG-act trough levels 10% above baseline until study completion.[39]

Although continuous therapy restored fertility for this patient, it may not effectively restore fertility for all patients with genitourinary lesions. Women with genitourinary lesions that appear ligneous should be tested for PLGD, and early treatment may preserve fertility. Therapy was continued during pregnancy to prevent fetal loss; treatment was effective and safe without adverse effects. Further experience with IV PLG concentrate use during pregnancy is needed and should involve a detailed discussion with the patient to review potential risks and benefits. Monitoring trough PLG-act levels during pregnancy is necessary due to increased plasma volume, especially during the third trimester, which may alter the pharmacokinetics and necessitate dose adjustments. Pregnant women and their obstetricians should coordinate with hematologists at an HTC to ensure effective dosing is maintained.

Case 6: Multiorgan involvement

A 25-year-old woman, diagnosed with PLGD at the age of 2 years (PLG-act 29%), presented with ligneous gingival lesions 1 to 2 cm in length, a left turbinate lesion, chronic hoarseness, and chronic vaginal and uterine lesions. Multiorgan involvement, including bilateral LC onset shortly after birth and repeated lesion stripping, was reported. At age 5, asthma-like symptoms developed and remained persistent. She experienced recurrent ligneous tonsillitis (Figure 7) since age 7, requiring prolonged hospitalization due to eating/swallowing difficulties necessitating IV FFP treatment that resulted in symptom resolution. Vocal cord lesions developed at age 14, and at age 20 she experienced complete aphonia for an extended period, after which her voice remained husky. At age 19, cervicitis and endometritis were noted, and she experienced irregular menstrual cycles despite use of oral contraceptives, significant dysmenorrhea, and postcoital bleeding. Urethral lesions were noted at the same age following recurrent cystitis unresponsive to antibiotics. At age 20, she experienced nasopalatine duct cyst removal with a history of gingival and nasal lesions. At age 22, polycystic ovaries were documented.

Multiorgan involvement in PLGD

While LC is the most common and well-recognized PLGD manifestation, multiorgan involvement has significant potential for systemic effects and is not correlated with PLG-act/ag levels. Symptom severity and range vary widely with an unpredictable clinical course. The overall health and symptoms of PLGD patients require close monitoring, irrespective of PLG-act/ag levels.

The initial treatment regimen was 6.6 mg/kg every 3 days for 12 weeks, followed by 6.6 mg/kg every 4 days. After the first dose of IV PLG concentrate, the patient passed a large vaginal lesion. After 6 months of therapy, no further episodes of conjunctivitis occurred, bronchodilators were not required, and gingival, vocal cord and nasal lesions resolved. Additionally, normal menses occurred with resolved dysmenorrhea. Gynecological follow-up scans and colposcopy revealed a normal cervix, uterus, endometrium, and ovaries.

Suggested monitoring and follow-up for PLGD patients after diagnosis

Close monitoring and multidisciplinary care are essential for managing PLGD patients. Regular 6-month surveillance is recommended for comprehensive ROS in asymptomatic patients and those on prophylactic or intermittent plasminogen replacement therapy. Individuals on therapy may require more frequent monitoring to assess symptoms, disease response, and PLG-act levels and to adjust therapy as needed. Patients require comprehensive education on PLGD and its symptoms to preemptively report potential issues such as viral infections, eye, and respiratory symptoms, or planned interventions, including dental procedures or surgeries, to ensure timely evaluation and care coordination. Although a specific case is not presented, the authors have personal experience utilizing more intensive dosing during surgical procedures and acute events, including daily dosing for 3 days, starting the day of the procedure, followed by every other day dosing until discharge or healing has occurred. Such procedures have included shunt removal and replacement, bronchoscopies, and port placement/removal. Minor

procedures, such as dental procedures, can be managed with a dose on the day of the procedure, and standard intervals thereafter. Tranexamic acid use is typically contraindicated in PLGD patients.

Special considerations

- Pediatric patients' dosages are adjusted based on weight; close monitoring for dose adjustments is essential.
- Intensified replacement therapy is performed before, during, and after surgical procedures to ensure appropriate wound healing.[26,40,51]
- During pregnancy, increased monitoring and potentially more frequent dosing may be necessary.[39]
- Women of childbearing age can use a contraceptive while on IV PLG concentrate therapy. Any form of contraception can be utilized during replacement therapy because PLGD is not a thrombotic disorder.

Ongoing studies in PLGD

The HISTORY study,[52,53] a 3-year retrospective and prospective investigation, aims to better characterize disease course, evaluate the diagnostic value of advanced coagulation assays, and explore the genetic basis of phenotypic variability. The study will include 100 PLGD patients and their first-degree relatives, making it the largest study cohort. A biobank

has been established to support future research, including identifying modifying factors for disease manifestation.

Optimizing PLGD management involves monitoring IV PLG concentrate pharmacokinetics (PK). WAPPS-Hemo,[53] created for hemophilia treatment, was adapted for PLGD to collect real-world PK data and treatment responses. A "disease burden" field has been included to individualize treatment plans (Figure 8).

PLGD awareness within the medical specialties

The challenge of educating diverse medical specialties regarding ultra-rare disorders like PLGD stems from the infrequency of clinical exposure combined with the initial variable sites at presentation. Specialists such as ophthalmologists and dentists may have less experience with interdisciplinary management approaches required for ultrarare diseases. Additionally, rare disorders may have limited coverage in standard medical curricula or continuing medical education programs. Addressing this knowledge gap requires developing targeted educational resources, multidisciplinary case discussions, and collaborative guidelines to ensure that even rare disorders are considered in diagnostic evaluations of specialists who may encounter them. Once a clinician is aware of the disorder, resources are available from online platforms, including the Rare Coagulation Disorders Resource Room, National Organization for Rare Disorders, UpToDate, Orphanet, and Partners in Bleeding Disorders Education.

Discussion

These cases underscore the complexities and challenges associated with PLGD and highlight the necessity for a multidisciplinary approach to effectively manage this condition. Each case illustrates distinct manifestations and complications, revealing the broad impact of this genetic disorder on various organ systems.

Case 1 presents a 14-year-old adolescent boy with recurrent LC, a common manifestation of PLGD. Despite <2% PLG-act, this patient developed LC in 1 eye at the age of 7 years. This case highlights the knowledge gap concerning the correlation between PLG-act levels and symptom severity, calling for improved monitoring and understanding of individual patient needs. Additionally, it underscores the need for including this ultra-rare disorder in the differential diagnosis.

Case 2 features a 37-year-old woman with severe respiratory complications stemming from PLGD. Her history of chronic cough and findings of ligneous lesions in the bronchial tree underline the critical nature of respiratory tract involvement, which may occur in 20% to 30% of PLGD patients. The delayed diagnosis and management of her respiratory symptoms resulted in chronic sequelae and life-limiting complications, emphasizing the need for heightened awareness and earlier intervention among healthcare providers.

In case 3, a 4-year-old girl diagnosed with PLGD after her brother's confirmation illustrates the importance of genetic counseling for families affected by this autosomal recessive

condition. The case underscores the necessity for preemptive monitoring of siblings to facilitate early diagnosis and management of potential complications, demonstrating successful intervention following the identification of gingival lesions.

Case 4 explores gastrointestinal manifestations in a 16-year-old adolescent girl who presented with symptoms consistent with IBD. Her treatment trajectory highlights the complications of managing concurrent gastrointestinal issues in a patient with PLGD and the importance of dual therapy approaches.

Case 5 focuses on a 33-year-old woman with extensive symptomatology, including fertility issues linked to uterine lesions. This case illustrates how PLGD complicates not only the management of LC but also reproductive health. The patient's experiences call for coordinated care among hematologists and obstetricians to effectively address the unique challenges of PLGD dosing during pregnancy.

Last, case 6 features a 25-year-old woman exhibiting multiorgan manifestations of PLGD, including gingival, respiratory, and genital involvement. This case reinforces the necessity for ongoing medical oversight and the importance of adjusting treatment protocols tailored to the evolving clinical picture experienced by patients with PLGD. Additionally, this patient presented with a PLG-act of 29%, highlighting the knowledge gap between activity levels and clinical severity.

Identifying factors contributing to symptom variability, including age of presentation or affected physiological system, despite similar PLG-act levels or identical *PLG* variants is essential to advance our understanding of this rare disorder. Insights will emerge from research identifying disease triggers and other genetic modifiers of disease expression. Development of severity categories will improve treatment guidance, including continuous versus intermittent prophylaxis. Addressing knowledge gaps is essential to enhance individualized management strategies to prevent long-term complications and optimize outcomes (Table 2).

Conclusions

The approval and availability of the first systemic targeted treatment have markedly enhanced our capacity to manage this condition effectively. As IV PLG concentrate is currently approved only in the United States, many patients with PLGD worldwide remain in urgent need of treatment. Expanded access will alleviate suffering, increase utilization reporting, and contribute to a greater understanding of IV PLG concentrate use and benefits.

PLGD presents a complex medical condition requiring a systematic approach optimally within a medical home, such as an HTC, to facilitate the best use of replacement therapy and its monitoring and coordinated care with other specialists as required. Treatment strategies should be personalized, considering each patient's manifestations and response to therapy. HTCs provide expertise and resources to administer infusions of replacement

products in a controlled setting, along with training for safe and effective home-based infusion management. Multidisciplinary care, regular monitoring, and prompt adjustments in therapy are essential to achieve optimal outcomes.

Clinicians who suspect PLGD should partner with HTCs to confirm diagnosis, contribute to research and data collection, utilize the WAPPS-Hemo PLGD PK module, and advocate for approval and availability of IV PLG concentrate in regions where it is inaccessible.

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Contributions: A.D.S. and C.N. wrote, edited, and approved the final manuscript.

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Table 1. IV PLG concentrate for plasminogen replacement therapy

Initial infusion dosage	6.6 mg/kg body weight every 2-4 days*
Duration	Depends on: • Initial disease burden • Area affected • Interference with organ function • Presence of long-term sequela
Monitoring during initial infusion	Initial infusions should be performed in a setting where monitoring for adverse events is performed during and up to 4 hours after infusion as: • In young children with respiratory lesions and small airways, lesions may slough and obstruct airways, leading to significant respiratory compromise or obstruction • Infusion-related adverse events such as anaphylaxis have been rarely reported • Rarely, IV PLG concentrate may cause bleeding at lesion sites as lesions slough†
Surgical interventions	Surgical interventions to remove lesions should only occur with IV PLG concentrate treatment to prevent rapid recurrence or further complications
Long-term therapy	Typically needed to maintain plasminogen levels in patients with: • A long history of continuous disease manifestation • Multiple system involvement • Presence of disease-related morbidity
Continuous prophylaxis	Patients with: • Significant respiratory lesions • CNS lesions (e.g., hydrocephalus requiring shunting) • Renal impairment • Persistent recurrent lesions after treatment withdrawal
Supportive care to alleviate patient symptoms	Lubricating or cyclosporine eye drops Maintaining regular dental hygiene to minimize oral lesions Providing respiratory support for airway complications

*An online pharmacokinetic system named WAPPS-Hemo (https://www.wapps-hemo.org/) has recently developed a specific monitoring module for plasminogen replacement therapy. This system has the advantage of limited time point testing with the development of a pharmacokinetics curve that can be utilized to determine the expected trough for each patient's infusion dose and interval; in addition, it can be used to modify dose and interval for treatment to achieve a targeted trough.

†Bleeding at lesion sites during or after infusion does not require intervention other than observation.

Table 2. Knowledge gaps regarding PLGD

Issue	Consequence
Disease rarity	Most medical providers unfamiliar with PLGD presentation Significant delay in diagnosis Multisystem manifestations not consistently evaluated or identified Insufficient data to define severity categories and predict disease course ○ Results in inability to determine requirement for continuous prophylaxis versus intermittent treatment
Lack of national systematic data collection for PLGD	Data collection often retrospective and incomplete, subject to error Lack of defined data points for systematic collection Lack of prospective systematic data collection results in inability to advance care and knowledge
Systematic retrospective and prospective data on PwPLGD and first-degree family members have not been collected	Inability to determine why siblings with same genetic defect may be asymptomatic Inability to determine effects of: ○ Genetic changes that cause deficiency ○ Plasminogen level ○ Sex and disease manifestation ○ Other genetic modifiers of disease expression ○ Environmental factors impacting disease expression ○ Impact of level of other coagulation factors, inflammatory polymorphisms
Inability to predict disease course	Knowledge of why symptoms remain persistent, or wax and wane is limited Phenotypic disease expression not correlated with plasminogen activity or genetic alteration Multiorgan involvement cannot be predicted
Lack of therapeutic care guidelines for different clinical circumstances	Inability to determine optimal targeted level and length of therapy for interventions and ongoing care Impact of specific treatment regimens on outcomes including quality of life of PwPLGD not defined or understood

PwPLGD, persons with type 1 plasminogen deficiency.

Figure Legends.

Figure 1. The history of PLGD and treatments.

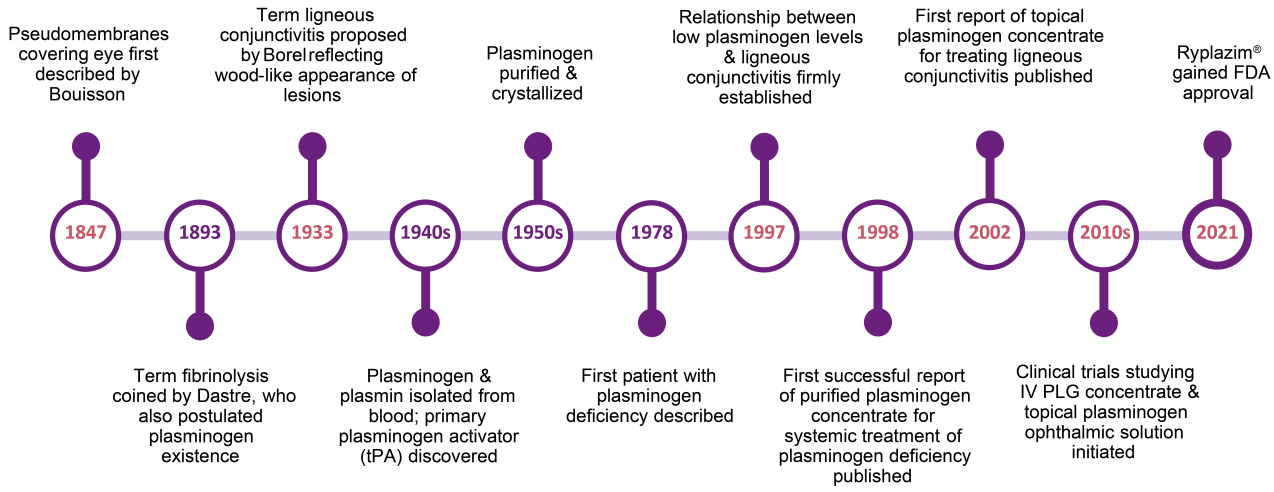
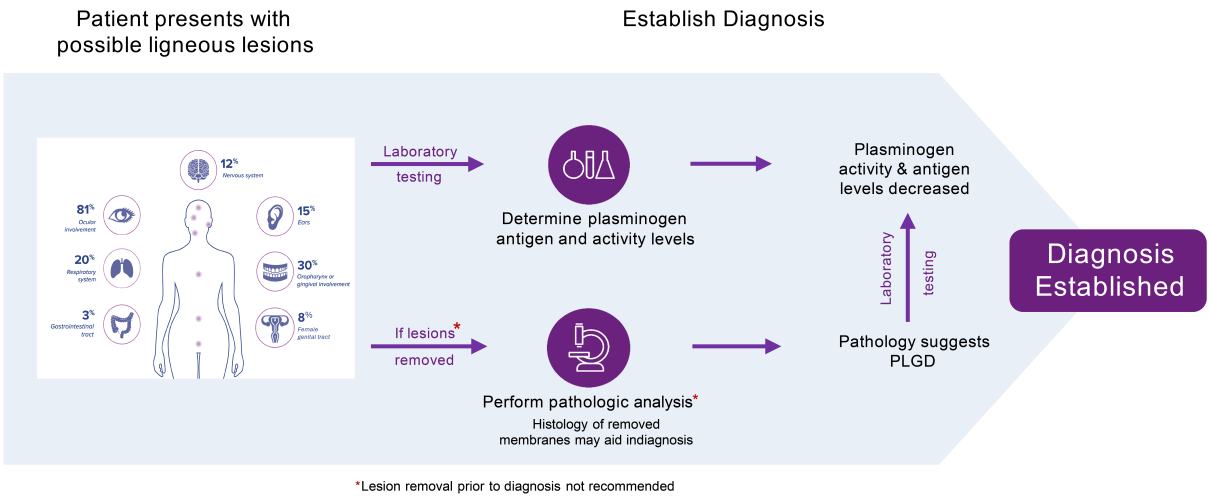


Figure 2. PLGD diagnosis.



*Lesion removal prior to diagnosis not recommended

Figure 3. Manifestations of PLGD.

System	Ophthal-mologic	Oropharynx	Respiratory	Auditory	CNS	GYN	Urinary	GI
Prevalence	81%	30%	20%	15%	12%	8%	4%	3%
Example	Ligneous conjunctivitis	Ligneous gingivitis	Pneumonia, airway obstruction, voice loss	Chronic otitis media, hearing loss	Congenital occlusive hydroceph-alus, Dandy Walker malformation	Dysmen-orrhea, vaginitis, cervicitis	Kidney stones	Duodenal ulcer
Sequelae if untreated	Blindness	Gingival tissue, bone and dental loss	Chronic respiratory compromise, airway obstruction, death	Hearing loss	Recurrent shunt obstruction, death	Infertility	Renal obstruction, impairment, failure	Possible association with IBD

CNS, central nervous system; GYN, gynecologic; GI, gastrointestinal; IBD, inflammatory bowel disease.

Figure 4. Ligneous conjunctivitis.

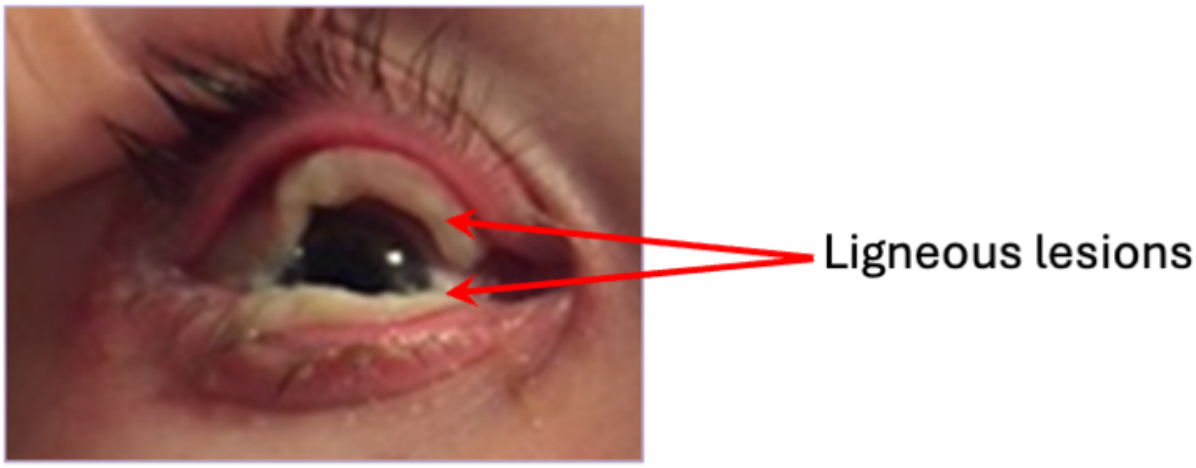
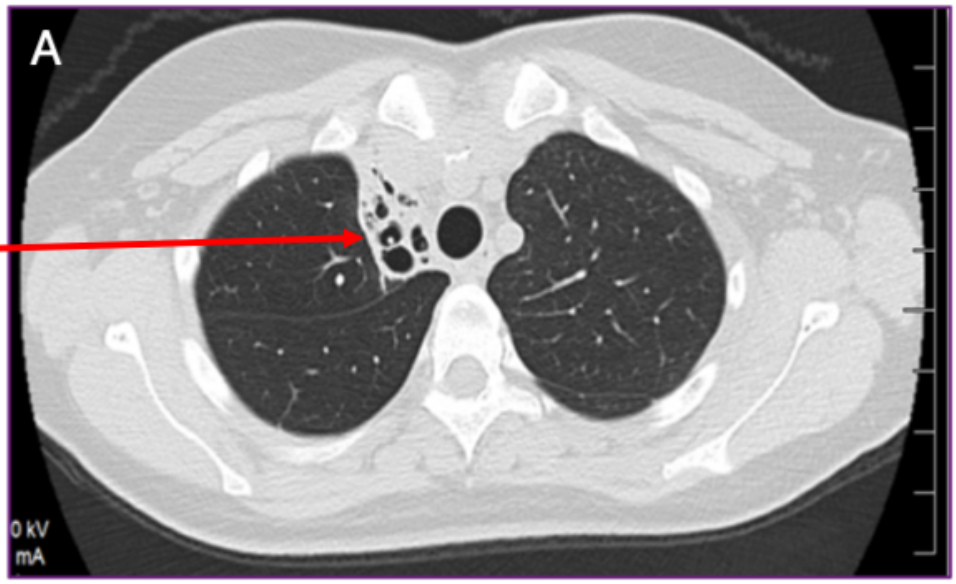
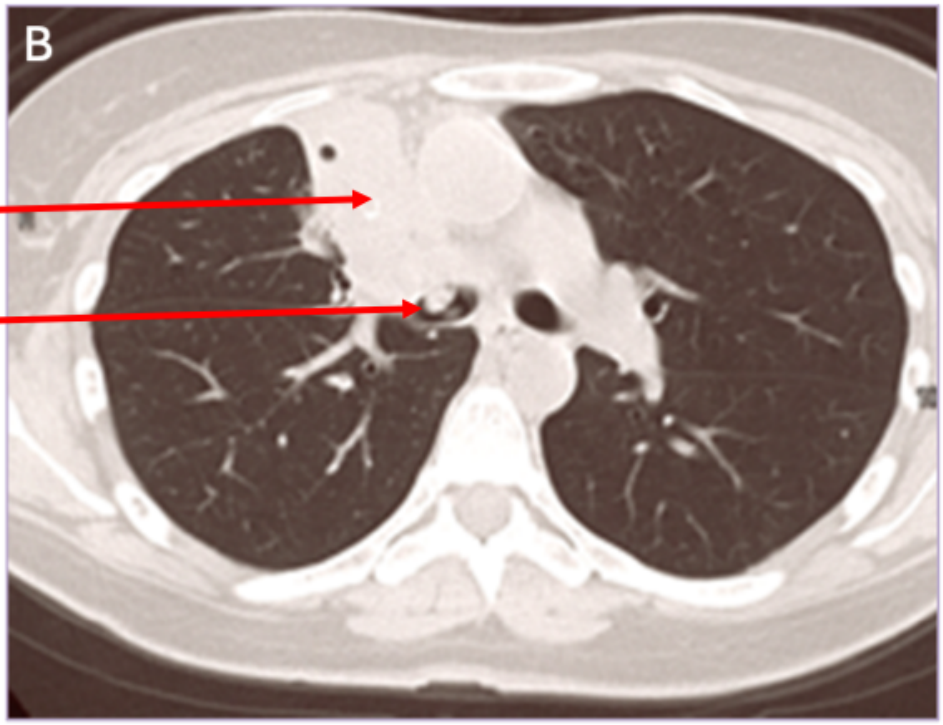


Figure 5. High-resolution computed tomography of the bronchus.



Chronic right upper lobe atelectasis with severe bronchiectasis (Age 26)



Consolidation of the right upper lobe with ligneous lesion in the bronchus intermedius (Age 35)

Figure 6. Gingival lesions in an adult.

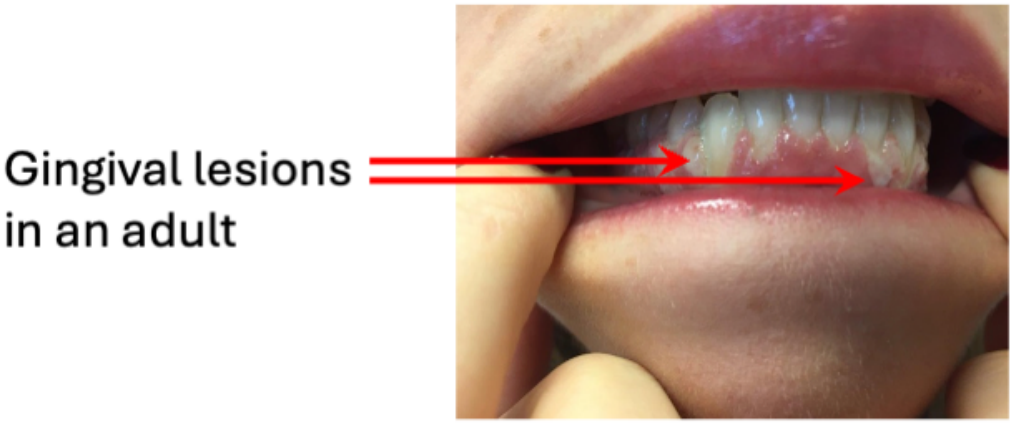


Figure 7. Ligneous tonsillitis.

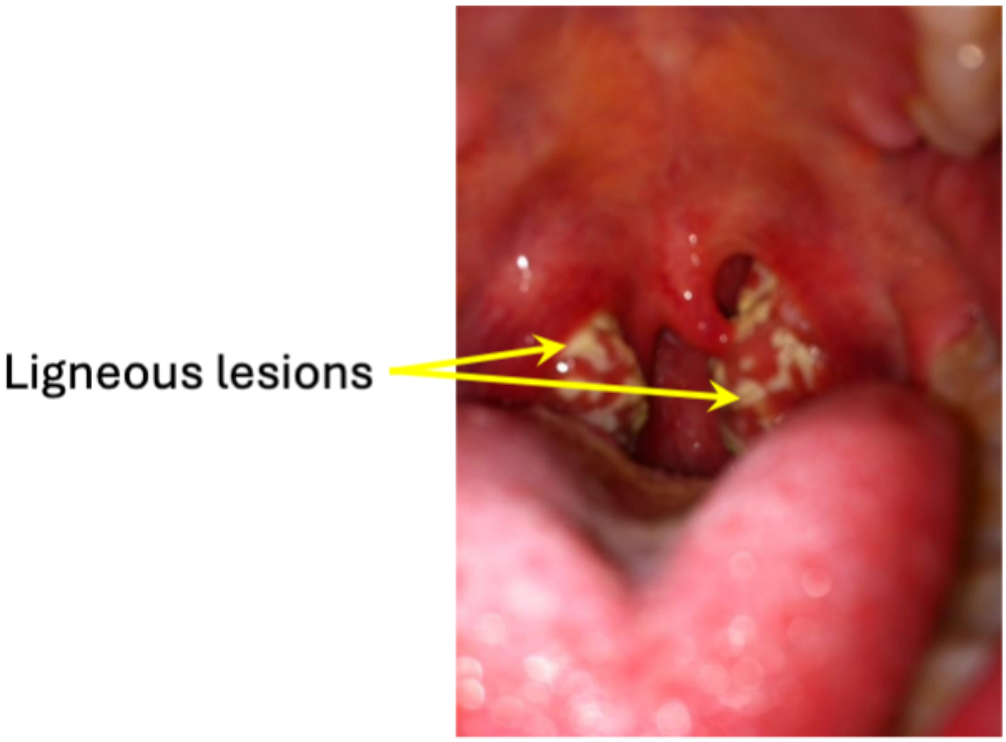


Figure 8

Disease burden category	Signs & symptoms
Mild	• Disease in remission • Disease without a current clinical manifestation • Single area with early onset (new gum lesion, new eye lesion, etc.)
Moderate	• One organ affected without significant clinical compromise • Only organ affected is eyes • Only gingiva affected
Severe	• Multi-organ disease (respiratory & genitourinary; eyes & respiratory, etc.) • One organ affected with significant clinical consequences (respiratory with clinical sequelae, renal with renal compromise, central nervous system disease with need for shunt, recurrent shunt obstruction malfunction with or without systemic manifestation)