



Hysterectomy-Induced Vesicovaginal Fistula Repair Using Platelet Rich Plasma: A Case Report and Narrative Review

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Abstract

A vesicovaginal fistula (VVF) occurs when a connection develops between the bladder and the vagina, and the gold standard treatment is surgical closure. Published data have demonstrated that most of the cases of VVF in developed countries had a surgical etiology, most commonly a hysterectomy. The most common symptom associated with VVF is continuous leakage of urine through the vagina. Here we present the case of a 49-year-old female from Puerto Rico with a 1-year history of involuntary urinary leakage. She was evaluated due to recurrent VVF status post two surgical repairs in the last year after abdominal hysterectomy. After cystoscopy and identification of a 5 mm vesicovaginal fistula in the posterior bladder, platelet rich plasma was injected without the need of surgical intervention with excellent results. To the best of our knowledge, this is the first documented case of hysterectomy induced VVF repair using only platelet rich plasma in a Puerto Rican patient.

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Background

A genitourinary fistula is defined as an abnormal anatomical anastomosis between the urinary and genital systems. This abnormal connection can involve either the ureter, bladder, or urethra in connection with the vagina, cervix, or uterus; the most common being a vesicovaginal fistula. A Vesicovaginal Fistula (VVF) occurs when a connection develops between the bladder and the vagina. Although the true prevalence in the developing world is unknown, mostly due to underreporting or go unrecognized, genitourinary fistula is considered a major morbidity in developing countries with a prevalence as high as 124 in 100,000 [1].

Vesicovaginal fistula can be either congenital or acquired, with congenital etiologies being extremely rare and commonly associated with other urogenital conditions. In developing countries, 70-95% of cases are acquired and related to an obstetric etiology, mostly due to prolonged obstructed labor. During an obstructed labor, there is a mechanical problem, malpresentation or disproportion that is not allowing the fetus to be delivered through the pelvis and vaginal canal despite adequate uterine contractions. This leads to continuous pressure from the fetus against the soft tissue of the vaginal wall and bladder which may lead to necrosis and a fistulous tract formation between both organs [1,2]. In developed countries, where obstet-



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ric services are accessible and protocols are established to detect and manage protracted labors in a timely fashion, fistulas due to obstetric causes are uncommon [1,3]. In contrast, VVFs are rare in developed countries and arise mainly as a complication during pelvic surgery, malignancy, or radiation therapy. Published data have demonstrated that 83.2% of cases of VVF in developed countries had a surgical etiology, most commonly a hysterectomy; It is estimated that 0.5-2% of hysterectomies are complicated by VVFs. This mostly occurs due to unnoticed injury to the bladder during surgery [3].

The most common symptom associated with VVF is continuous leakage of urine through the vagina. The amount of leakage may vary depending on the size and location; a small fistula may only present symptoms while the patient is voiding [4]. The formation of fistulas may vary depending on the etiology; they can occur as fast as one to two weeks after the insult, especially if they are due to pelvic surgery or an obstetric complication; some may take years to develop, primarily if it is caused due to radiation therapy [1,4]. Multiple modalities may be used to diagnose a vesicovaginal fistula, but a thorough physical evaluation is of the utmost importance. The location, size, and the number of fistulous tracts will determine the management route. When there is uncertainty of the origin of vaginal fluid, a measurement of the fluid's creatinine content can be performed, and elevated concentrations are consistent with urine. If the fistula is not identified during physical evaluation, a "tampon test" may be performed. A tampon or gauze is placed in the vagina, and a solution of methylene blue (turn urine blue) is placed in the bladder using a transurethral catheter; the patient is asked to ambulate, and if the tampon or gauze is blue stained upon removal, it is highly indicative of a VVFs formation [1]. A cystourethroscopy, which could be combined with vaginoscopy as well, is another vital modality used in the diagnosis and surgical planning of VVFs; it helps determine its location and bladder mucosa viability. An important aspect during the workup and evaluation of a patient with a VVF is determining if there is concomitant ureteral involvement. This could be done during the "tampon test" previously described, in conjunction with ingestion of oral Pyridium, which turns urine orange; if the tampon is orange stained upon removal, it may indicate the presence of a ureterovaginal fistula as well [5]. Other modalities often preferred are imaging studies, such as a CT scan with IV contrast, X-Ray studies, such as intravenous pyelography, retrograde pyelography, and voiding cystourethrography, or sonography, such as transabdominal sonogram with color doppler [1].

We reported a case of a 49-year-old female from Puerto Rico, who presented with a 1-year history of involuntary urinary leakage due to recurrent vesicovaginal fistula.

Materials and methods

A narrative review was conducted by searching through PubMed, Scopus, and Clinical Key. Search terms included: vesicovaginal fistula, platelet-rich plasma injection, PRP, hysterectomy-induced fistula, wound healing, and tissue repair with different combinations to find as many recently peer-reviewed original research articles as possible. The article selection was made using the following criteria: recently peer-reviewed articles including reviews, case reports, clinical trials, meta-analysis, and systematic reviews concerning hysterectomy-induced vesicovaginal fistula and platelet-rich plasma injection. Articles published in English between the years 1979 to 2022 on human subjects were included in the review.

Main Results- Case presentation

Case of a 49-year-old from San Juan, Puerto Rico who came to the Gynecology Clinic with a complaint of failure to control urine in the last year. She was evaluated due to recurrent vesicovaginal fistula status post two transabdominal repairs in July 2019 and November 2019 after abdominal hysterectomy done in February 2019. She has been having urinary incontinence with a constant dribble that needs pad changing every 15-30 mins since February 2019. Urine incontinence worsened with erect position, physical activity, coughing, and sneezing. She denied profuse vaginal bleeding, abnormal discharge, or pelvic pain, and she was sexually active.

At time of surgery, vital signs were within normal range. Her abdomen was soft and depressible, with no tenderness and no palpable mass. On genitourinary evaluation, the patient had normal external genitalia with urine-soaked vulva. After spinal anesthesia, the patient was placed in a lithotomy position and prepped and draped in the usual sterile fashion. During cystoscopy, bilateral ureteral orifices were observed and a vesicovaginal defect of 5 mm in diameter located on the posterior bladder was identified. Posterior bladder wall vesicovaginal fistula was catheterized with an open-end catheter. Attention was placed to the vaginal vault and fistulous tract was dissected using sharp dissection. A small bladder stone was observed and removed from the tract. After cystoscopy and identification of the vesicovaginal fistula, whole blood was collected in the usual sterile fashion technique. The collected blood was placed in the Eclipse PRP system centrifuge per product protocol. Blood was collected with an anticoagulant such as citrate, a calcium chelator, to prevent spontaneous blood clotting and consequent platelet activation. Subsequently, whole blood was centrifuged to separate red blood cells, followed by centrifugation to concentrate platelets. The autologous platelet-rich plasma (PRP) preparation was achieved via the Eclipse PRP system manufactured by Eclipse Med. Activation of PRP in our study is accomplished without exogenous substances by relying on shear force from injection and exposure to native collagen at the injection site. PRP was injected at 6 points around the edge of the fistula. Transvaginal injections were successfully placed using Eclipse's kit needle. Adequate hemostasis was noticed. Patient received Ciprofloxacin 500mg BID for a total of 5 days and Oxybutynin 5 mg TID until postoperative evaluation in two weeks. At the end of the procedure 16F foley catheter was left in place. The patient was discharged home the same day of the procedure and the catheter was removed after two weeks.

The patient made an uneventful postoperative recovery. In the follow up visit, physical examination and cystography was normal. The fistula was closed and the vaginal wall at the site of the procedure healed without any signs of scarring, redness, or granulosa tissue. Moreover, the patient did not complain about any urinary difficulties or urinary tract disorders. She remains well after two years postoperatively.

Discussion

Small (<3-5mm), non-malignant, and early detected fistulas can be managed conservatively. Keeping a urethral catheter for 0.5-2 months along with anticholinergics treatment might be helpful in spontaneous closure of these fistulas. For small fistulas with a late diagnosis, electrocoagulation of the mucosal layer along with catheterization for 2-4 weeks could lead to closure of the fistula [6]. In most cases these conservative measures fail, and surgery is required. The choice of surgical repair

depends on the surgeon's experience, the location and size of the fistula, and the patient's preference. If the tissue around the fistula is presenting inflammation, edema, infection or necrosis, surgery should be delayed up to 2-3 months until healthy tissue compromises the surrounding tissue. The gold standard for VVF treatment is surgical closure and can be performed transvaginally, transabdominally, or laparoscopically. VVF is most commonly repaired transvaginal, as most gynecologists find this approach more convenient [7]. When a vesicovaginal fistula repair approach is analyzed, there are several factors to take into consideration. Vaginal incisions can be done immediately in the absence of infection or other complications, contrast to abdominal incisions that often are delayed 3 to 6 months. The exposure of the fistula is crucial to decide which approach is needed. Even if the fistula tract is located near ureteric orifice, reimplantation may not be necessary in transvaginally incision. The type of adjunctive flaps can change between abdominal and vaginal incision. The omentum, peritoneal, and rectus abdominis flap can be used in the abdominal approach whereas the labial fat pad (Martius fat pad), peritoneal flap, gluteal skin, or gracilis myocutaneous flap are usually used transvaginally. Moreover, transabdominal approach is indicated for large fistula, location high in a deep narrow vagina, radiation fistula, failed transvaginal approach, small-capacity bladder requiring augmentation, need for ureteral reimplantation, and the inability to place patient in the lithotomy position [7]. The successful closure rate for a first attempt is 85% [8]. Frequency, urgency, urge incontinence, stress incontinence are complications of VVF repair. Stress incontinence most likely occurs in obstetric fistula in which injury involves the sphincter. Anticholinergic drugs might be helpful in reducing the symptoms. They should be given to patients who have bladder spasms, as these not only cause pain, but might also compromise healing [9].

Failure of VVF repair and recurrence occurs in 30% of cases. It is recommended that recurrent cases should be dealt with a gap of at least 3 months from the previous attempt of repair [10]. This suggests that our patient was treated according to the guidelines established. Still, recurrence remains a highly distressing complication. A multivariate analysis reported that recurrence was statistically significant for multiple fistulas (single vs two or more), fistula size (>10mm), fistula type (type I vs type II), fistula etiology (obstetrical vs non-obstetrical) and the presence of urinary tract infection before the repair [11]. This study also reported that the interposition of flaps was a protective factor for recurrent cases. Since the VVF of our patient did not fulfill these parameters, we can speculate that the recurrences presented in our case could be associated with other factors such as comorbidities.

Invasive procedures such as transvaginal and transabdominal surgery have been widely studied, whereas less attention has been paid to the use of Platelet Rich Plasma (PRP). Nowadays, this less invasive approach is offering promising results and additional benefits to surgeons and patients considering the simplicity of technique, high success rate, minimal blood loss, low postoperative morbidity, and shorter time required for operation and postoperative recovery [12]. Platelet-Rich Plasma (PRP) has been found to enhance regeneration and repairing capacity of different tissues. In PRP therapy, growth factors released from platelets α -granules, accelerate stages of healing processes, provide tissue necrosis resolution, chemotaxis, cell regeneration, cell proliferation and migration, extracellular matrix synthesis, remodeling, angiogenesis, and epithelialization. Its mechanism of action is mostly based on stimulating the syn-

thesis of matrix metalloproteinases, increasing cutaneous fibroblast growth as well as the production of extracellular matrix components including type I collagen and elastin [13]. PRP is already used in a wide range of disciplines with beneficial effects. The abundant use of PRP in regenerative medicine has forced obstetrics and gynecology to put it into practice as well, particularly in reproductive medicine. Studies have revealed the effectiveness of PRP in endometrial abnormalities. PRP has been associated with an increase in endometrial receptivity and a consequent increase in implantation rates [14], as well as being effective for endometrial growth in patients with thin endometrium [15]. Since 1979, several methods and different plasma concentrates have been used as salvage treatment for urogenital fistula [16,11,17,18,19,20]. Successful closure of VVF has been reported in only one study using PRP injection and platelet-rich fibrin glue without any other additional surgical procedure [11]. Likewise, our case report presented here, demonstrated a successful vesicovaginal fistula repair using platelet rich plasma without the need of surgical intervention.

A multicenter study concerning hysterectomies revealed that VVF developed after iatrogenic bladder injury during hysterectomy was associated with larger uterus, longer surgery time, and more severe bladder injuries [21]. Since it is well documented that VVF development days after surgery is caused from tissue ischemia due to trauma during operation, additional healing-enhancing techniques should be involved in the treatment of recurrent VVF. Our outcomes are similar to previous studies concerning the treatment of VVF [9]. We expected that regeneration of tissues around the fistula using PRP injections was going to stimulate the healing processes after its surgical closure. To achieve proper neovascularization and prepare the surrounding tissue, we injected PRP in 6 points around the edge of the fistula prior to surgical closure. In contrast, other studies report successful closure by interpositioning fibrin glue transvaginally into the fistulous tract and blocking the vaginal orifice of the fistula with a collagen injection [22]. This might be an option for small fistulas with a relatively long tract, but in the case of hysterectomy induced VVF, the fistulous tract is usually very short, and the diameter is usually greater than 5 mm, as the scaring tissue shrinks after each previous surgery and pulls the edges away from the center [21]. Those specific conditions prevent fibrin glue deposits from adhering to the surrounding tissue and enforcing the fistula closure.

Regardless of two previous surgical interventions, our patient continued to present recurrence of VVF. Based on these findings, we can speculate that the patient's comorbidities could be playing a more significant role in the fistula's wound healing and postoperative recurrence. Our patient reported a past medical history of Diabetes Mellitus, hypertension, history of heavy drinker, and non-alcoholic fatty liver disease. Therefore, a better understanding of the influence of these comorbidities on wound repair could help us establish an underlying mechanism linking risk factors with VVF recurrence. It is known that microvascular dysfunction and imbalance in the cytokine profile caused by high glucose burden might be considered as the major reason for the chronic, delayed, and even nonhealing wounds in diabetes mellitus patients [23,24]. Moreover, diabetic wound fluid contains a large number of proteases such as metalloproteinases, which cause degradation of some growth factors, which further impedes angiogenesis and wound healing [25]. Assessment of the relationship between hypertension and wound healing is indicated since cardioprotective medications may have effects on coagulation or clotting cascades. Thus, it

should be noted that our patient was taking Losartan and Amlodipine, which are associated with decreased platelet activity and coagulation factors in a dose- and time-dependent manner [26,27]. Clinical evidence and animal experiments have shown that exposure to alcohol impairs wound healing, specifically the proliferative phase, and increases the incidence of infection. Animal studies have demonstrated that exposure to alcohol can impair re-epithelization, angiogenesis, and wound closure [28]. The ethanol-mediated decrease in wound vascularity causes increased hypoxia and oxidative stress. Connective tissue restoration is also influenced by ethanol exposure, and results in decreased collagen production and alterations in the protease balance at the wound site [29]. As discussed, there are many local and systemic factors that can interfere with one or more phases in the wound healing process, thus causing impaired tissue repair. These important considerations should be taken into account in the clinical management of VVF repair.

Notably, the case report presented here is based on a Puerto Rican female and comorbidities such as diabetes and cardiovascular disease are the leading causes of death in Puerto Rico and US [30,31]. Factors such as blood glucose and blood pressure come into play in negatively modulating the healing process. Together, these preventative factors could be predisposing this population to the development of fistulas. Given the upward trend in cases of diabetes and hypertension in these populations, prevention and management strategies are crucial to reduce the burden of these comorbidities.

Conclusions

Through this case report and narrative review, we have highlighted the most important factors affecting the VVF formation and recurrence. Such factors demonstrated the imperative need to assemble a more comprehensive understanding to the extent of comorbidities and treatment approaches. This case report demonstrated the efficacy of PRP as a single therapy for treatment of recurrent VVF after a previous unsuccessful attempt to close the fistula with conservative surgical approach. Our case report is quite encouraging, especially in complicated cases of recurrent VVF. In conclusion, PRP injections seem to be both effective and safe according to the published data and our case report and could be offered as a novel procedure for the treatment of VVF.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author contributions

AB designed the study, led the search, primary analysis, and manuscript development. IS and DS assisted in the study design, analysis, and manuscript development. JR and FS assisted in manuscript review and editing. All authors read and approved the published version of the manuscript.

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Disclosure

The authors declare that they have no competing interests.

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This study did not require ethical approval.

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