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Necrotizing Fasciitis in the Puerperium of a Woman with Complement Deficiency: Case Report and Review Literature

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Abstract

Complement deficiencies are uncommon types of primary immunodeficiency. Necrotizing fasciitis is a rare complication in pregnancy characterized by soft tissue invasion and necrosis of the subcutaneous and other adjacent tissues, leading to high mortality rates. We report a case of a 29-year-old pregnant woman with functional deficiency of the C4 complement component and short uterine cervix. Admitted at the hospital with preterm labor, she received multiple doses of immunoglobulin. After 8 weeks, she had a premature membrane rupture, and due to pelvic presentation she had a cesarean. The patient presented multiple obstetric complications, such as operative wound infection, endometritis, sepsis, necrotizing fasciitis and pelvic septic thrombophlebitis. She underwent multiple antimicrobial schemes, a hysterectomy and 4 extensive debridements of the abdominal wall because of significant necrosis. She stayed at the hospital for 101 days (32 of those in ICU in immediate postpartum). 41 days after cesarean, patient was discharged in good conditions. Our case emphasizes individual handling and high multiple doses of immunoglobulin for favorable outcome of the case.

Keywords

Pregnancy, Immunodeficiency, C4 Factor, C4 Deficiency, Necrotizing

Fasciitis, Puerperal Infection

1. Introduction

The complement system plays an important role in the innate and adaptive immune response against pathogens. It is essential for removing damaged cells, avoiding infections by enhancing the ability of clearing microorganisms and helping the modulation of the immune response [1]. Complement deficiencies are rare, with a worldwide prevalence of 0.03% [2], and predispose bacterial infection and/or autoimmune diseases. Individuals with abnormalities in the early components of the complement (especially C1q, C2 and C4) have a minimum risk of infection but a high risk of developing autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Increased susceptibility to these diseases is related to the inefficient removal of immune complexes [3], and C4, part of the classical complement pathway, is closely linked to the removal of these complexes and of apoptotic debris [4].

In patients with C4 deficiency, the main treatment is based in the use of immunoglobulin, which helps reducing the frequency and severity of infections. Intravenous preparations start with 400 - 600 mg/kg every 3 to 4 weeks and are almost exclusively made of IgG [5] [6]. Monitoring of IgG levels should be performed every 3 months and should remain above 500 mg/dL. Most adverse effects are related to infusion rate, most commonly being fever, tremors, arthralgia, myalgia, abdominal pain, nausea and headache. Fatal events are rare and can be prevented by careful medical supervision and early management [5] [6].

We report a case of a pregnant woman with C4 deficiency with multiple previous gestational losses. She progressed during the puerperium to septic pelvic thrombophlebitis and necrotizing fasciitis in the abdominal surgical wound. She had a good evolution and was discharged without sequelae. This case involves two rare pathologies, without previous reports in literature of simultaneous occurrence and survival: immunodeficiencies of complement factors and necrotizing fasciitis. In reporting the case, we intend to help management of similar cases that may occur. The case occurred in the Hospital de Clínicas de Porto Alegre, in the state of Rio Grande do Sul, Brazil—a public-private institution linked to the Universidade Federal do Rio Grande do Sul.

2. Case Report

Patient has consented to the disclosure of her case for academic and scientific purposes. Pregnant woman, 29 years old, white. Obstetric history of six pregnancies—two vaginal deliveries and three abortions. The two vaginal deliveries had neonatal death, weighting 498 grams (gestational age of 22 weeks) and 650 grams (gestacional age of 25 weeks). In both cases, she was hospitalized after

rupture of the membranes and labor was induced. The abortions occurred in the first pregnancy trimester. Cerclage was performed in the third and fourth gestation, however they both evolved with ovular infection and gestational loss after two weeks. The patient hadn't used immunoglobulin in any previous gestation. She had a sister with history of multiple gestational losses and a father which died of sepsis after thoracic trauma. Both of them had C4 deficiency.

First prenatal consult happened at 15 weeks, when progesterone 200 mg/day was prescribed and serial measurements of the uterine cervix by transvaginal ultrasound were programmed. The uterine cervix was measured biweekly until 22 weeks, being initially 37 mm and progressing to 24 mm, when Ingamed® cervical pessary was inserted.

The patient was hospitalized at 21 weeks due to a vaginal infection, receiving clindamycin, azithromycin and metronidazole, Use of vaginal progesterone was maintained and a 5-day pulse of intravenous immunoglobulin was initiated. The patient's evolution followed as described in the table below.

Day of Hospitalization Gestational age	Evolution and management
D1 to D6 20w5d to 21w3d	Treatment with antibiotics was maintained. Received pulses of intravenous (IV) immunoglobulin for 5 days. Cervical length: 24 mm.
D7 to D20 21w4d to 23w3d	Nifedipine for tocolysis and prophylactic enoxaparin were started. Negative urinalysis and normal morphological ecography.
D21 to D36 23w4d to 25w6d	Indomethacin for tocolysis at D21. At 24 weeks, two doses of intramuscular betamethasone were prescribed. New pulse of IV Immunoglobulin for 5 days. Obstetric ultrasound with fetus on percentile 10 and normal Doppler.
D37 to D53 Gestational age: 26w to 28w	Third pulse of IV Immunoglobulin for 5 days. Intravenous Salbutamol was used for contractions. At 26 weeks, new dose of Indomethacin for 2 days for tocolysis.
D54 to D59 28w to 29w	Due to increased vaginal discharge, Azithromycin and Ampicillin were prescribed. Reapplication of intramuscular betamethasone at 28 weeks and suspension of Nifedipine. Premature rupture of membranes at 28 + 4 weeks (D57). Removal of cervical pessary. Bacteriological of the vaginal secretion showed Klebsiella, **Enterococcus** and Citrobacter. C-section is indicated due to pelvic presentation and labor onset.
D60 to D63 29w to the 2nd day of puerperium	Cesarean section at 29 + 1 weeks. Female newborn, 1400 grams. Treatment for vaginal discharge with Cefepime, Amikacin and Clindamycin was started. Feverish peaks in first day of puerperium, with normal chest X-ray and leukocytosis. New dose of IV Immunoglobulin is administered and previous antibiotics are exchanged for Vancomycin and Meropenem. Because of severe sepsis and probable puerperal endometritis, patient is transferred to the Intensive Care Unit (ICU). Ultrasound of the abdomen showed heterogeneous contents in the uterine cavity. Diagnosis of septic thrombophlebitis.
Day of Hospitalization Day of Puerperium	
D64 to D68 3rd to 7th day	Discharge from ICU at D64 of hospitalization. Full dose of unfractionated heparin for pelvic septic thrombophlebitis was started. New febrile peaks despite use of Meropenem and Vancomycin. Worsening of the medical condition, with increased vaginal bleeding and pain on mobilization of the uterine cervix and at decompression of left iliac fossa. Surgical wound infection (**Figure 1**) Hysterectomy with bilateral salpingectomy and left oophorectomy was performed at D68.

Continued

D69 to D70 7th to 8th	Use of IV Immunoglobulin and full anticoagulation with unfractionated heparin infusion pump. New fever peak in the first postoperative day, operative wound with hyperemia and drainage of serohematic secretion. Amikacin was added to the scheme with Vancomycin and Meropenem. Patient continues to be feverish and leukocytosis worsens (33,000). Abdominal tomography showed signs of thrombosis in the right gonadal vein, grouped fluid collections with gaseous bubbles permeating next to the infraumbilical anterior abdominal wall musculature, and small accumulation of fluid and densification of adipose planes in the pelvis. Operative wound evolved with necrosis, crepitation and fluctuation. Amikacin is suspended and Polymyxin B is initiated for necrotizing fasciitis.
D71 to D75 9th to 13rd	First debridement of the operative wound, with purulent discharge and muscular involvement (Figure 2). **Negative culture of abdominal wall necrosis for coagulase-negative Staphylococcus.** Patient stays at ICU in the postoperative period. Polymyxin B, Clindamycin, Vancomycin and Meropenem were maintained, and unfractionated heparin was reinstated. New febrile peak at D6 post hysterectomy, elevation of C-reactive protein and leukocytosis. Operative wound with blisters, exudate and fibrin. Fluconazole is initiated. New worsening of the medical state.
D76 to D79 13th to 16th	New debridement (Figure 3) of operative wound in D9 post hysterectomy showed bullous areas at its borders, rectus abdominis muscle with infiltration, areas of purulent suppuration and accumulation of devitalized tissue at the lower edge of the wound. Retraction of left rectum muscle and removal of left bullous areas was performed until viable tissue was found. Fluconazole, Clindamycin, Polymyxin B, Meropenem and Vancomycin maintained. Intubation is necessary at D11 post hysterectomy. Worsening of the suprapubic and lateral infiltrate of the operative wound, with extension to the left iliac fossa and inguinal region, where areas of necrosis with blisters were found. New febrile peak and worsening of renal function. A dose of immunoglobulin and a new debridement in postoperative D11 were prescribed.
D80 to D86 17th to 22th	Patient returned from debridement in severe septic shock. She was in mechanical ventilation requiring increasing doses of vasopressin and hydrocortisone. Hemodialysis was started. In postoperative D13, new debridement of surgical wound and vacuum dressing exchange. Patient showed hemodynamic improvement, when sedation was paused and vasopressors were suspended. Hemodialysis stopped at D18 after hysterectomy.
D87 to D100 23rd to 40th	Patient is discharged from ICU at postoperative D25, hemodynamically stable and without vasoactive drugs. No signs of sepsis or organic dysfunction were found, and renal function was preserved. She was discharged from the hospital in postoperative D32 (D100 of hospitalization) using warfarin but without antibiotics. Her skin color was modified, with a darker shade than previously (Figure 4).
D101	Patient was discharged in good conditions.

W: weeks; D: days; IV: intravenous; ICU: Intensive Care Unit.

The patient used warfarin for three months and after four months the color of the skin returned to its usual color and the surgical scar was in the final stage of healing (Figure 5 & Figure 6). After 1 year, she returned without complications and her skin color had returned to its normal.

The newborn remained 53 days in the neonatal ICU, requiring mechanical ventilation and a nasogastric tube. He was discharged in good general condition along with the mother. He maintained follow-up visits, evolving without sequelae. Currently, he has a palatal hemangioma in regression.

3. Discussion

During pregnancy, the innate and adaptive immune system must be regulated to ensure the survival of the mother and the fetus. The complement system is a part

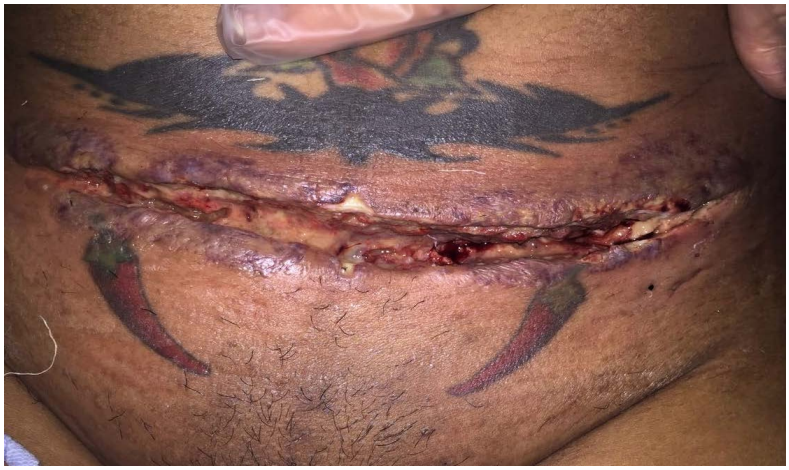

Figure 1. Initial wound infection.

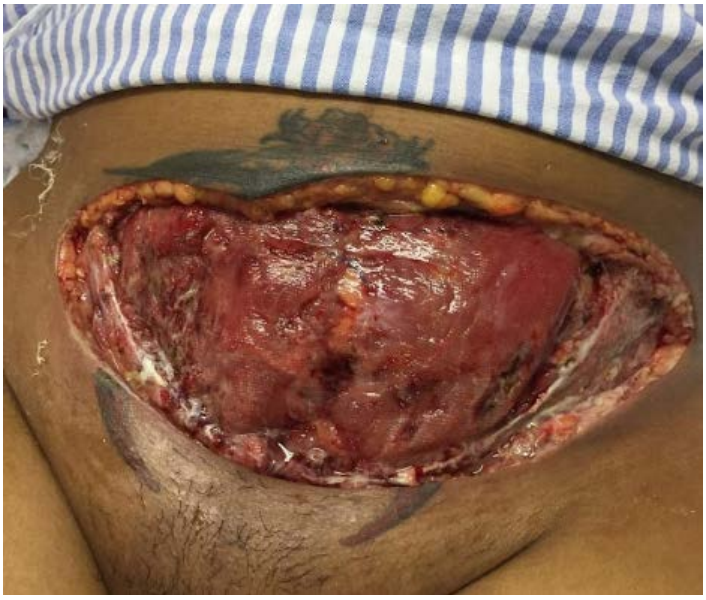

Figure 2. Patient with necrotizing fasciitis after first debridement.

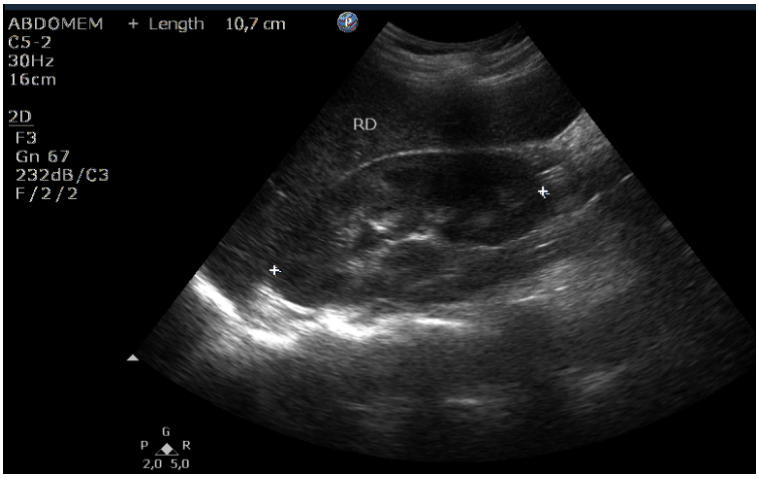

Figure 3. Abdominal ultrasound with heterogeneous contents in the uterine cavity.

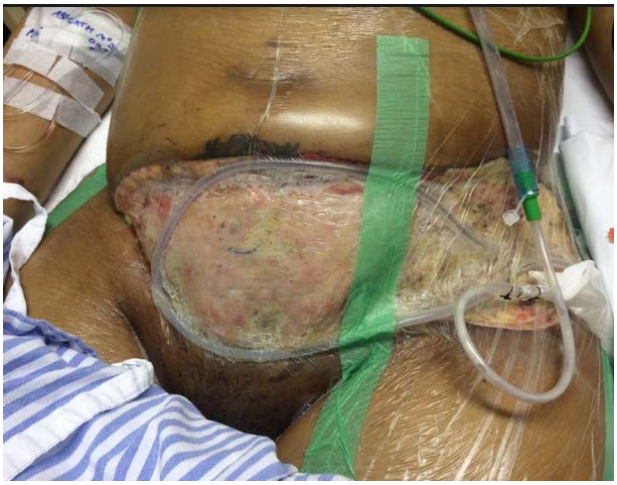

Figure 4. Patient with occlusive dressing after debridement.

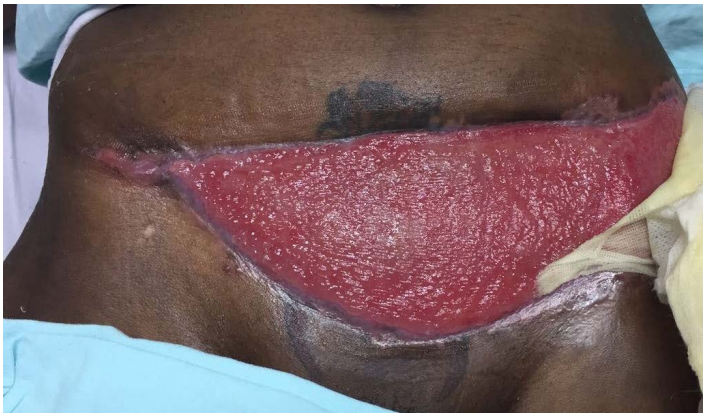

Figure 5. Operative wound with granulation tissue after 40 days of puerperium. Dullness of the patient's color due to the prolonged use of antibiotics.

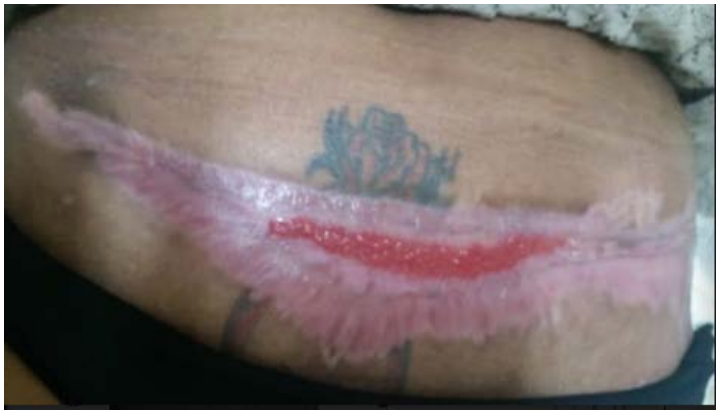

Figure 6. Patient 4 months after surgery. The color of the skin returned to its usual color.

of the immune system that consists of a set of proteins that act sequentially, providing a rapid and powerful defense to the body by identifying and destroying pathogens. Its inadequate activation can cause a number of complications.

More than 50 proteins constitute the complement system, and C4 is part of

the classical complement route. IgG and IgM antibodies bind to antigens and initiate a cascade of events, where the C1 factor cleaves C4 and C2 in C4b and C2b, respectively. These factors interact and form C3 convertase, which converts C3 to C3a (that produces inflammatory response) and C3b (that has an opsonization function). The addition of C3b to C3 convertase generates C5 convertase, which cleaves C5 to C5a and C5b. C5b then connects to C6 and C7, forming a complex that binds to the membrane. The C5bC6C7 complex binds to C8 and multiple C9, forming the membrane attack complex (MAC). This complex forms a channel that allows the free diffusion of substance, disrupting the cellular osmotic balance and leading to death of the invading organism [7].

Inherited complement deficiencies are rare [2], corresponding to 4.9% of all primary immunodeficiencies [8]. The most common one is C1 deficiency, occurring in 0.01% of the population [9]. Severe deficiencies of complement proteins predispose to infections, mainly by encapsulated bacteria such as Streptococcus pneumoniae. In addition, C1, C2, and C4 deficiencies may predispose to autoimmune diseases, primarily collagen vascular diseases and systemic lupus erythematosus. This is due to failure in removing immune complexes and necrotic material. More than 75% of patients with C4 deficiency have some manifestation of autoimmunity [10]. Studies have shown that patients with C4 deficiency have a decrease in regulatory T cells, which are important to prevent the appearance of aberrant autoimmune responses [11]. Complete homozygosity for C4 deficiency is rare. The C4 gene is located on chromosome 6p21.3, and there are two isotypes of the gene product (C4A and C4B5). Healthy individuals usually have two copies of each of the isotypes, while those with less than four copies of C4 are more likely to develop autoimmune diseases [4] [12].

Pregnancy alone can increase infection by suffering various mechanical and physiological adaptations and by creating an immunosuppressive state. These changes in a patient with deficiency of complement factors—important in regulating the immune response—play a prominent role in severe infections and subsequent sepsis [13]. Infections are the fifth leading cause of maternal death [14].

Necrotizing fasciitis (NF) is an invasive and potentially lethal soft tissue infection. It is characterized by necrosis of the subcutaneous tissue, superficial fascia and other adjacent tissues. The infection can involve epidermis, dermis, subcutaneous tissue, fascia and muscle. It is considered a surgical emergency, with mortality exceeding 40% [15] and increasing incidence in recent years [16]. Pregnancy, delivery and gynecological procedures are important risk factors for NF. Other risk factors are those that predispose infections, such as peripheral vascular disease, diabetes mellitus, impaired immune system, and surgical procedures that compromise skin integrity. In a retrospective study with 23 patients with NF in lower abdomen or pelvis, 34.7% had diabetes [17]. Obesity, which increases the infection risk during pregnancy and cesarean delivery, is also an important risk factor [18].

The fasciitis can be divided considering microbiology or presence of gas in the tissues. Polymicrobial fasciitis is caused by anaerobic and aerobic bacteria, with typically at least one isolated anaerobic (*Bacteroides*, *Clostridium* or *Peptostreptococcus*) in combination with enterobacteria (*Escherichia coli*, *Enterobacter*, *Klebsiella*, *Proteus*). Monomicrobial fasciitis is usually caused by Staphylococcus, or group A and other beta hemolytic Streptococcus. Pure myonecrosis by *Clostridium perfringens* has a more homogenous muscle invasion and a higher rate of mortality, being the only one that needs to be differentiated from other necrotizing soft tissue infections [4]. The incidence of this type of NF varies from 0.3 to 15 per 100,000 people.

Main manifestations of NF include severe pain, edema, erythema, fever, crepitation and epithelial necrosis. The disease has rapid onset and progression, involving mainly the vulva, perineum, lower limbs and abdominal wall. Skin involvement is usually smaller than the extent of necrosis in the underlying tissue, turning the differentiation between NF and cellulitis difficult [19]. Definitive diagnosis occurs after surgical debridement, with microbiological and histological evaluation of the infected tissues. Imaging findings precede skin involvement, aiding in diagnosis. Magnetic Resonance imaging can determine the extent of inflammation in the fascia and necrosis of infectious tissue [20]. Crepitation, presence of gas in soft tissue or bubble formation in imaging have a good sensitivity for diagnosis [4]. Among laboratory tests, base deficit and blood lactate are often elevated. Without rapid and efficient intervention, NF quickly leads to septic shock, multiple organ failure and death. Most of the time, this illness requires long hospitalization, days in ICU and high hospital expenses [16].

Prognosis in NF depends on rapid diagnosis and aggressive multidisciplinary management, involving deep debridement of all necrotic tissue, intravenous antibiotics, appropriate analgesia and intensive care in ICU [19]. Antibiotics are administered empirically before culture results and can be adjusted later according to the antibiogram. It should cover gram positive cocci, enteric gram negative rods and anaerobics. Daily evaluation of the open wound and surgical debridement until the infection is no longer perceived decreases mortality [15]. Normally, the procedure is repeated every 2 days until there is no evidence of necrotic tissue. Closure of the wounds begins as soon as possible, just when the viable tissue allows the skin to be re-approximated or grafted [19]. Hyperbaric oxygen therapy has been used adjuvantly, and although it does not decrease mortality, it can accelerate wound closure. This technique improves oxygen supply to compromised ischemic tissue, increases phagocytosis of polymorphonuclear cells, acts as a bactericidal agent for anaerobic organisms and can disrupt the production of alpha toxin. However, studies validating this therapy are still lacking [21].

The use of IV Immunoglobulin also appears to be beneficial for the survival of patients with NF [19]. Human Immunoglobulin can be beneficial in primary immunodeficiencies, such as those caused by absence of B cells or inefficient production of antibodies, and primary defects with hypogammaglobulinemia.

Currently, there is sufficient clinical evidence showing that Immunoglobulin decreases frequency and severity of infections and of hospitalizations in patients with primary immunodeficiencies. However, much of this evidence refers to immunodeficiencies that compromise the production of antibodies (the most prevalent ones). There are no studies showing benefits of using IV Immunoglobulin in patients with complement deficiency; however, the lack of other treatments for this disease and the good results in other immunodeficiencies justify its use in patients with C4 deficiency.

The appropriate dose of immunoglobulin for primary immunodeficiencies is still being studied. An initial dose of 400 - 600 mg/kg is advised every 3 to 4 weeks. The frequency of adverse effects ranges from 0.6% to 30%, being higher in the presence of infections or at the first infusion [22]. This is due to the formation of antigen-antibody complexes, which can be reduced if the patient is afebrile or using antimicrobials. To reduce adverse effects, infusion should be slow and by infusion pump. During the infusion, most common symptoms include tremors and fevers (mimicking infection), abdominal pain, nausea and headache. In these cases, the infusion should be discontinued and the symptoms managed.

In necrotizing fasciitis, IV Immunoglobulin also appears to be beneficial. It is supposedly able to inhibit the mitogenic activity of bacteria, especially gram positive. In addition, Immunoglobulin can block T lymphocytes activation by bacterial antigens, decreasing the production of inflammatory cytokines [23] [24].

4. Conclusion

Complement deficiencies are extremely rare conditions that are associated with the development of autoimmune diseases. In pregnancy, an immunosuppressive state alone, they can cause numerous adverse outcomes. Necrotizing fasciitis is an infection that has immunosuppressive states as an important risk factor. The reported case shows how immunocompromised pregnant women need follow-up in high-risk prenatal care and, if possible, the use of prophylactic IV Immunoglobulin. In cases of infection, rapid diagnosis and multidisciplinary therapy, with a surgical approach and use of antibiotics, are important. We emphasize the importance of immunoglobulin use for the patient's excellent outcome and the relevance of knowing family history and efficacy of immunoglobulin use in other relatives. A clear understanding of the role of the complement system in pregnancy—and its possible deficiencies—is necessary to prevent adverse outcomes. No cases of patients with both necrotizing fasciitis and C4 immunodeficiency have survived. We believe that future cases may benefit from the successful management of this patient using immunoglobulin.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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