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CASE REPORT

Impaired Wound Healing Following Free Flap Breast Reconstruction in a Patient Treated with Fremanezumab: A Case Report and Implications for Perioperative Management

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ABSTRACT

This case report explores the potential effects of fremanezumab, a calcitonin gene-related peptide-targeting antibody used for migraine prevention, on postoperative wound healing. To our knowledge, this is the first documented case of a female experiencing delayed wound healing after receiving fremanezumab following a free flap breast reconstruction. The patient, who tested positive for the BRCA gene mutation, underwent a bilateral prophylactic nipple-sparing mastectomy with a transversus rectus abdominis muscle flap reconstruction. Initially, recovery was uncomplicated, but severe skin necrosis and blistering were noted at the first postoperative visit. The condition worsened, requiring topical treatments and sharp debridement. Despite low-grade fevers and prophylactic antibiotic treatment, no infection was formally confirmed. Frequent debridement was necessary for several months. By five months postoperatively, the breasts and most abdominal wounds had healed. This case underscores the need for heightened clinical awareness, suggesting a potential association between fremanezumab and impaired wound healing. This observation has significant implications for perioperative patient management. Notably, while there is a potential link between fremanezumab and the impaired wound healing observed in this case, a direct causal relationship remains unconfirmed. It is crucial to carefully balance the risks of delayed wound healing with the potential for worsened disease control. This consideration is especially important when using biologic agents for chronic conditions. Each case should be evaluated individually to tailor the best treatment approach.

INTRODUCTION

Calcitonin gene-related peptide (CGRP) is a vital vasoactive component of the trigeminovascular system. It plays a crucial role in the pathogenesis of migraine attacks when present in the bloodstream [1]. The development of CGRP monoclonal antibodies has pioneered a novel class of prophylactic treatments for chronic migraine [2]. Beyond its neurological impact, CGRP is also critical for wound healing. It promotes revascularization by upregulating vascular endothelial growth factor, decreases levels of inflammatory mediators such as tumor necrosis factor-alpha and macrophages, and stimulates proliferation of keratinocytes [3]. Consequently, deficiencies in CGRP can significantly impair wound healing processes.

The association between impaired wound healing and CGRP monoclonal antibodies is underscored by a case involving a 51-year-old migraine patient treated with erenumab [3]. Following minor injuries, this patient experienced severe wound healing complications, with biopsy results revealing extensive skin inflammation and vessel thrombosis. While this case highlights the potential side effects associated with erenumab, the impact of fremanezumab on wound healing remains less defined.

The clinical trials evaluating fremanezumab, detailed in its package insert, consisted of two multicenter, randomized, three-month, double-blind, placebo-controlled studies [4]. These studies, however, excluded patients with major cardiovascular or thrombotic conditions such as cerebrovascular accidents, transient ischemic attacks, deep vein thrombosis, or pulmonary embolisms. This exclusion highlights significant safety data gaps for patients with vascular disorders and those undergoing surgeries with major vascular implications. This underscores the imperative for targeted, comprehensive research.

We present a case of significantly impaired wound healing in a patient with chronic migraines treated with fremanezumab. This occurred following autologous free flap breast reconstruction after a bilateral mastectomy. To our knowledge, this is the first reported instance of wound healing delays linked to fremanezumab in breast reconstruction. The case underscores the urgent need for heightened clinical vigilance and suggests a potential connection between fremanezumab and delayed wound healing. It also calls for further research into its perioperative impacts.

CASE PRESENTATION

A 48-year-old woman with a history of chronic migraines has been under management with fremanezumab since May 2021 for her condition. Following a positive test for the BRCA gene mutation, she consulted a plastic surgeon regarding preventive breast surgery. She subsequently underwent bilateral prophylactic nipple-sparing mastectomy with muscle-sparing transversus rectus abdominis muscle flap reconstruction. Notably, she did not present with conventional risk factors for poor wound healing such as obesity, smoking, or corticosteroid use.

Her regimen of monthly fremanezumab injections for chronic migraines continued uninterrupted in preparation for the elective surgery, spanning approximately 15 months prior to the procedure. Initially, her postoperative period was uneventful, and she was discharged on the

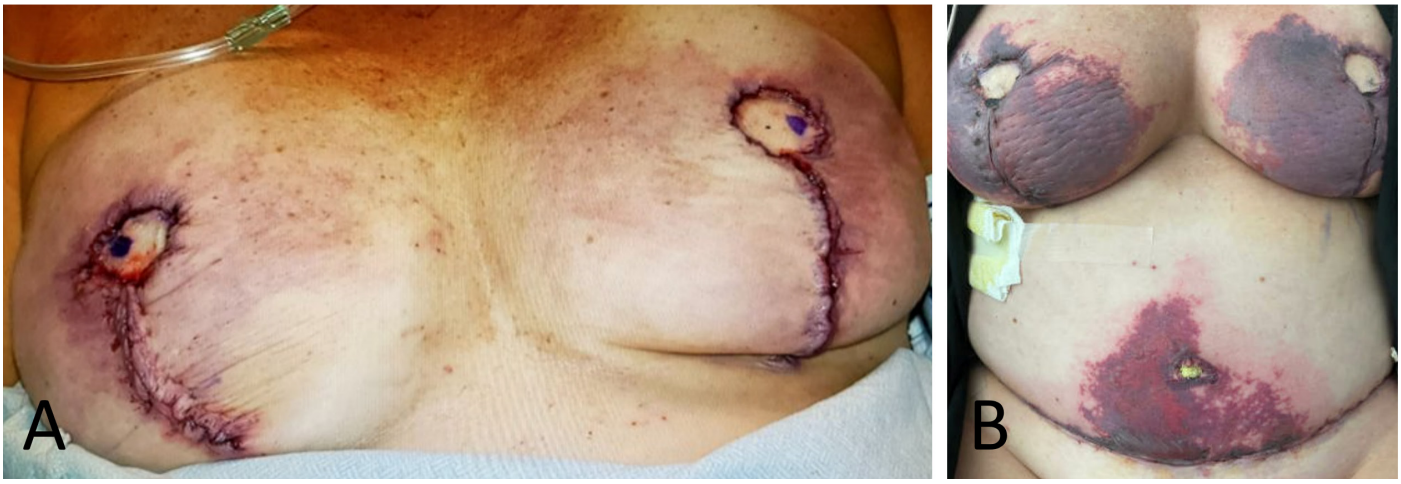

Figure 1. Initial and one-week postoperative observations following bilateral prophylactic mastectomy and reconstruction. (A) Immediately after surgery, this panel shows the surgical results of a bilateral prophylactic nipple-sparing mastectomy complemented by transversus rectus abdominis muscle flap reconstruction. The incisions are notably clean, exhibiting no immediate signs of complications. Nonetheless, early bruising patterns on the skin hint at potential complications and the risk of subsequent skin necrosis. (B) At one week postoperative, the image reveals pronounced skin necrosis and blistering at both the bilateral breast incisions and the abdominal donor site, underscoring a significant impairment in wound healing.

third day without any immediate concerns for wound healing. However, early bruising patterns on her skin soon indicated potential complications, suggesting the possibility of future skin necrosis (Figure 1A). This led the surgical team to arrange close follow-up.

At her first postoperative examination one week later, significant skin necrosis and severe blistering at the incision sites were observed (Figure 1B). Subsequently, the wounds deteriorated further, exhibiting increased necrosis, purple discoloration, blistering, and sloughing (Figure 2). Consequently, treatment strategies were adjusted to include applications of Silvadene cream, Medihoney, and Hydrogel.

One month post-surgery, she developed low-grade fevers, prompting empirical treatment with doxycycline. As the fevers persisted, levofloxacin was administered to address potential Pseudomonas infections, despite the absence of confirmed cellulitis or surgical site infection. The extensive eschars over her bilateral breast and abdominal wounds eventually necessitated sharp debridement (Figure 3).

In the following months, she required frequent clinic visits for ongoing debridement of the wounds, particularly where exposed mesh was noted on the right side. Wound care strategies using Xeroform and calcium alginate were employed to facilitate epithelialization. By five months postoperatively, considerable healing had occurred; both breasts and the abdomen had nearly fully recovered (Figure 4).

DISCUSSION

This case study examines a middle-aged woman with a confirmed BRCA gene mutation who exhibited significant delayed wound healing and skin necrosis after undergoing prophylactic mastectomy and breast reconstruction. We hypothesize that this extensive skin necrosis and prolonged wound recovery may be associated with her treatment with fremanezumab for chronic migraines. This hypothesis is supported by three observations: firstly, the degree of delayed wound healing is unusual for uncomplicated free flap reconstruction cases; secondly, this patient lacked conventional risk factors for poor wound healing, such as obesity, smoking, or corticosteroid use; thirdly, the only variable that could influence wound healing was the use of the CGRP antagonist fremanezumab during the perioperative period. These factors suggest a potential link between fremanezumab use and the delayed wound healing observed, although a direct causal relationship has not been definitively established.

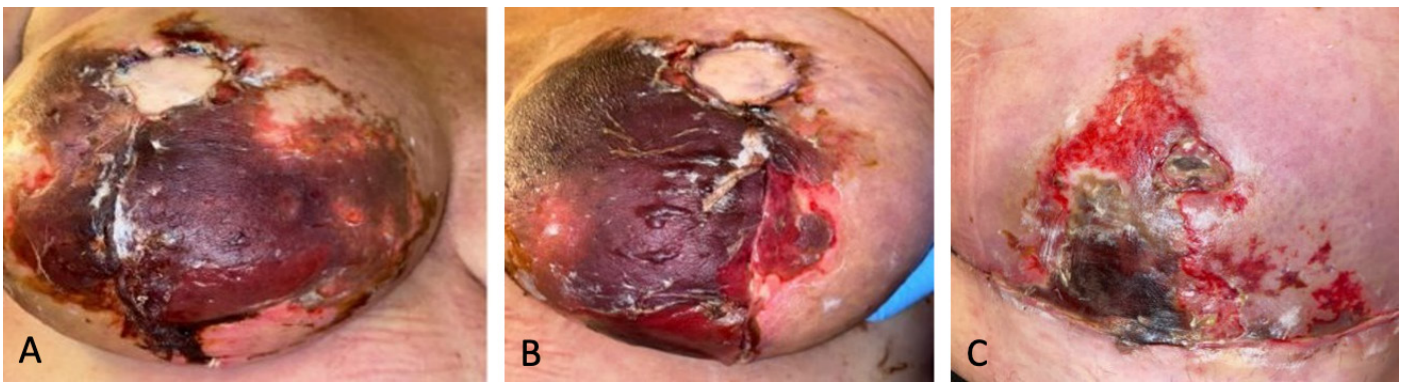

Figure 2. Evolving skin necrosis of surgical incisions. (A) Right breast showing increased necrosis and purple discoloration. (B) Left breast displaying extensive blistering and sloughing. (C) Abdominal donor site with significant necrosis and sloughing.

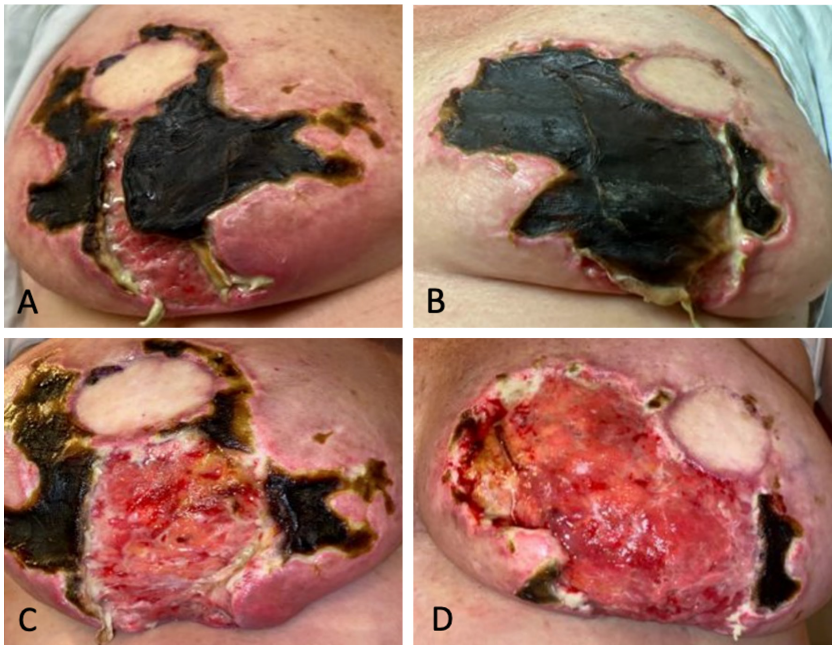

Figure 3. Management and progression of eschars one month post-surgery. (A) Prominent eschar formation on the right breast prior to surgical intervention. (B) Visible eschars on the left breast before debridement. (C) Post-debridement view of the right breast, revealing the underlying tissue. (D) Post-debridement appearance of the left breast, showing the necrotic tissue being removed.

Biologics and Surgery: Balancing Risks

The controversy surrounding the practice of stopping biologic medications before cosmetic, elective, or reconstructive surgery is multifaceted, involving the balancing of theoretical risks and practical patient outcomes. The perioperative management of biologic medications necessitates careful consideration of potential complications, such as delayed wound healing or postoperative infections, against the risk of exacerbating the underlying disease if the medication is discontinued.

The 2017 guidelines from the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons (AAHKS) recommend holding biologic medications as close to one dosing cycle as possible before elective procedures [5]. This recommendation is based on the understanding that immunosuppressive medications increase the risk of postoperative infections and complications. This guidance primarily focused on patients undergoing major surgeries like hip or knee arthroplasty.

However, recent studies challenge this approach. Notably, the Postoperative Infection in Inflammatory Bowel Disease (PUCCINI) trial involved 947 patients with inflammatory bowel disease across 17 sites [6]. It investigated the impact of preoperative tumor necrosis factor inhibitor (TNFi) exposure on postoperative infection risks. The study found that neither reported TNFi use within 12 weeks of surgery nor detectable serum TNFi concentrations were independent risk factors for postoperative infections, including surgical site infections. The results of this prospective cohort study suggest that preoperative TNFi treatment does not increase infection risks. Therefore, it should not influence surgical decisions for most patients with inflammatory bowel disease. This provides reassurance for continued use of TNFis close to surgical dates without heightened concerns for postoperative complications.

Additionally, a systematic review conducted by van Duren et al. revealed no significant increase in surgical site infections or delays in wound healing among patients who continued their biologic disease-modifying anti-rheumatic drugs during orthopedic procedures [7]. This analysis also highlighted the limited quality of evidence supporting the perioperative discontinuation of biologic agents, complicating clinical decision-making.

The updated 2022 guidelines from the ACR and AAHKS also reflect these evolving insights [8]. They recommend withholding biologic medications for a dosing cycle before surgery in patients with inflammatory arthritis, but allowing surgery to be scheduled after that dose. For severe cases of systemic lupus erythematosus, continuing biologics is advised, while in less severe cases, withholding biologics is recommended to avoid the risk of organ damage. The updated guidelines incorporate new immunosuppressive medications, highlighting the importance of shared decision-making between doctors and patients.

Discontinuing biologic medications can lead to significant flare-ups of the underlying disease, adversely impacting patient health and quality of life. This risk often outweighs the theoretical postoperative risks, such as delayed wound healing or postoperative infections. Additionally, recent studies indicate minimal perioperative complications with continued biologic use. Consequently, a more individualized approach is advocated, reflecting a shift towards tailored patient care based on the latest evidence.

Overall, the controversy remains due to the need for balancing theoretical risks with practical considerations and the evolving nature of clinical evidence. As new research continues to emerge, it is imperative for guidelines to adapt accordingly, ensuring optimal patient outcomes through personalized care strategies.

Overview of CGRP Monoclonal Antibodies

CGRP monoclonal antibodies, specifically erenumab (Aimovig®) [9] and fremanezumab (AJOVY®) [4], have recently emerged as effective and generally well-tolerated alternatives to traditional antimigraine medications. The United States Food and Drug Administration (FDA) approved erenumab in May 2018, followed by fremanezumab in September 2018, thereby setting significant benchmarks in the therapeutic landscape of migraine management [2].

Table 1 provides a comprehensive comparison of fremanezumab and

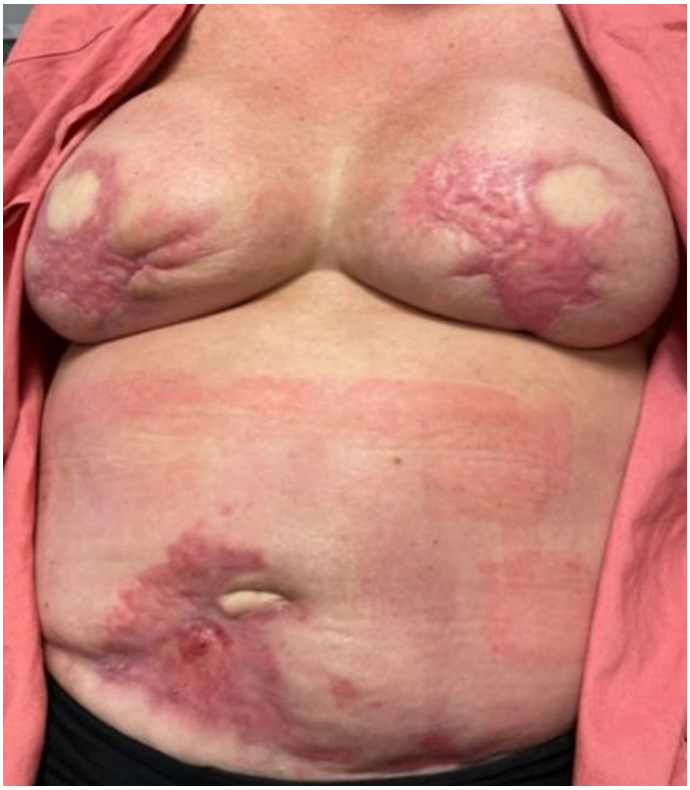

Figure 4. Comprehensive healing with contraction at five months post-surgery. This image displays substantial healing at the bilateral breast and abdominal donor sites. It highlights significant tissue recovery with noticeable contraction, illustrating the effects of the healing process on tissue morphology.

erenumab, detailing their targets, mechanisms of action, administration routes, dosage forms, common side effects, clinical indications, molecular composition, and half-lives. Fremanezumab targets the CGRP molecule directly, while erenumab targets the CGRP receptor. Both agents are administered via subcutaneous injection; fremanezumab offers monthly or quarterly dosing options, whereas erenumab is available in monthly doses. Notably, fremanezumab is a humanized monoclonal antibody containing some non-human components, while erenumab is a fully human monoclonal antibody, which reduces the risk of immune reactions. Fremanezumab has a half-life of approximately 31 days, while erenumab has a half-life of about 28 days.

CGRP Monoclonal Antibodies: Wound Healing Concerns

Despite their proven efficacy, these treatments exhibit minimal side effects, typically including constipation, muscle spasms, itching, injection site pain, nasopharyngitis, and upper respiratory tract infections [10]. Notably, the existing literature does not report any instances of impaired wound healing associated with these treatments in surgical settings. However, there have been two reported cases of non-surgical wound healing impairments associated with erenumab [3,11].

The first case involved a 51-year-old woman treated with erenumab for chronic migraines. She developed severe wound healing complications following a minor skin injury, raising concerns about the impact of the drug on wound recovery [3]. The second case described a 41-year-old woman, also treated with erenumab for chronic migraines, who experienced spontaneous bruising primarily on her lower legs and thighs [11]. The hypothesis for the ecchymosis in this patient suggests that CGRP function suppression by erenumab may delay capillary healing, leading to extensive blood leakage and visible bruising. Initially, this bruising was thought to be influenced by the concurrent use of fish oil supplements; however, it is more likely attributed to CGRP suppression rather than a direct interaction between erenumab and fish oil.

Both aforementioned cases are linked to erenumab use [3,11]. Conversely, there are no recorded instances of surgical wound healing complications associated with fremanezumab, particularly in the perioperative period. This report presents the first observed case of a female patient treated with fremanezumab for chronic migraines who experienced delayed wound healing following a free flap breast reconstruction.

Table 2 summarizes these three cases of CGRP monoclonal antibody use in chronic migraine treatment, highlighting wound healing complications linked to CGRP monoclonal antibodies. This comparative analysis underscores the necessity for cautious administration of CGRP monoclonal antibodies, especially in patients undergoing surgery. It also highlights the need for further research into their potential impacts on wound healing.

Labeling Gaps in CGRP Monoclonal Antibody Safety

The package insert for fremanezumab omits warnings about impaired wound healing or elevated infection rates. This omission likely stems from the exclusion of patients with significant cardiovascular or thrombotic conditions from key clinical trials, resulting in a noticeable gap in safety data for these groups [4]. Furthermore, the FDA approvals of erenumab and fremanezumab in 2018 highlight the novelty of CGRP monoclonal antibodies in clinical use [2]. This underscores that the development of comprehensive clinical experience is still ongoing. Consequently, as clinical use expands, it is crucial to monitor and document potential adverse effects rigorously. This approach helps fill existing knowledge gaps and ensures that all safety concerns, especially those related to wound healing and infection rates, are thoroughly addressed in future updates to drug labeling and clinical guidelines.

To address these gaps, this case report aims to supplement the safety data by exploring potential risks in patients undergoing major vascular surgeries. However, it is important to clarify that this report merely presents a clinical observation and does not establish a causal relationship between fremanezumab and delayed postoperative wound healing. The findings are offered as subjective interpretations and are not intended to prompt changes in drug labeling, as other factors could also influence these outcomes.

In light of this rare clinical scenario, it is imperative for healthcare providers to thoroughly assess potential confounding factors that may impact wound healing before administering fremanezumab. These factors include diabetes mellitus, vascular pathologies, persistent infections, conditions necessitating immunosuppression, malnutrition, chronic inflammatory disorders, tobacco use, obesity, psychological stress, and corticosteroid use. Meticulous evaluation of these variables is crucial to minimize any additional risk of delayed wound healing in patients treated with fremanezumab.

Study Limitations

This case report provides valuable insights into potential wound healing issues associated with fremanezumab, yet it has several limitations. The findings are based solely on a single patient's experience, significantly limiting their generalizability. Additionally, since the potential adverse effects of fremanezumab were not anticipated, the medication was not discontinued to assess symptom reversal. This ongoing use, without a trial of cessation, restricts clear interpretation and may influence the reporting of symptoms, reducing the ability to definitively link fremanezumab to the observed wound healing delays.

CONCLUSION

This article underscores the need for vigilance when administering CGRP monoclonal antibodies, such as fremanezumab, in perioperative settings.

Table 1. Comparison of Fremanezumab and Erenumab

Characteristic	Fremanezumab [4]	Erenumab [9]
Brand name	AJOVY®	Aimovig®
Target	CGRP itself	CGRP receptor
Mechanism of action	Binds to CGRP, preventing it from binding to its receptor	Binds to CGRP receptor, blocking CGRP from activating it
Administration	Subcutaneous injection	Subcutaneous injection
Dosage forms	Monthly or quarterly injections (225 mg monthly or 675 mg quarterly)	Monthly injections (70 mg or 140 mg)
FDA approval	September 2018	May 2018
Common side effects	Injection site reactions, constipation, upper respiratory infections, muscle spasms	Injection site reactions, constipation, muscle spasms, nasopharyngitis
Clinical indications	Preventative treatment of migraine in adults	Preventative treatment of migraine in adults
Molecular composition	Humanized monoclonal antibody	Fully human monoclonal antibody
Half-life	Approximately 31 days	Approximately 28 days

Abbreviation: CGRP, calcitonin gene-related peptide; FDA, Food and Drug Administration.

Table 2. Review of Wound Healing Impairments in Migraine Patients Treated with CGRP Monoclonal Antibodies

Variables	Case 1 (Current case)	Case 2 [3]	Case 3 [11]
Age, years	48	51	41
Gender	Female	Female	Female
Medication	Fremanezumab	Erenumab	Erenumab
Indication	Chronic migraine	Chronic migraine	Chronic migraine
Duration of medication use	15 months	6 months	12 months
Initial migraine frequency	Not specified	13 days/month	16 headache days/month, 12 migraine days/month
Treatment outcome	Effective for migraine	Reduction to 5 migraine days/month	Significant reduction in headache and migraine days
Wound healing impairment	Severe delayed healing after surgery	Severe impairment after trivial skin injury	Increased bruising tendency, extreme ecchymosis
Associated symptoms	Skin necrosis, blistering, skin sloughing	Deep perivascular and interstitial lymphohistiocytic infiltrate, edema, thrombosed vessels	Spontaneous bruising primarily on lower legs and thighs
Biopsy and histology findings	Not performed	Confirmed deep perivascular and interstitial lymphohistiocytic infiltrate, edema, ulceration, thrombosed vessels	Not performed
Other medications	Doxycycline, levofloxacin	Zolmitriptan, opipramol	Various antimigraine prophylactics, fish oil supplements
Pre-existing conditions	BRCA gene positive, prophylactic mastectomy	Severe migraine refractory to common treatment	Migraine without aura, rare occasional small bruises
Risk factors for poor wound healing	None (no obesity, smoking, corticosteroid use)	None (no obesity, smoking, peripheral vascular disease)	Fish oil supplements, no known coagulopathy
Clinical management	Silvadene cream, Medihoney, Hydrogel, debridement	Topical treatment with gentamycin, betamethasone, triamcinolone, clioquinol	Discontinuation of fish oil supplements
Outcome	Complete healing of breasts and abdomen	Healing with residual post-inflammatory hyperpigmentation	Improvement in bruising tendency after cessation of fish oil
Conclusion/Hypothesis	Delayed healing linked to fremanezumab use	Impaired wound healing possibly linked to erenumab	Ecchymosis likely from CGRP suppression, not erenumab and fish oil interaction.

Abbreviation: CGRP, calcitonin gene-related peptide.

It highlights rare but significant wound healing complications in surgical patients. While the impaired wound healing in the presented case may be linked to fremanezumab, a direct causal relationship is not established. Balancing the risks of delayed wound healing against worsened disease control when using biologic agents for chronic diseases is crucial. These risks should be evaluated on a case-by-case basis.

ARTICLE INFORMATION

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