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REVIEW BREAST

Red Breast Syndrome: A Review of Available Literature

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Abstract There is scant literature regarding a recently identified clinical entity termed red breast syndrome. Its clinical presentation has been described as a non-infectious, self-limited erythema of a post-mastectomy breast reconstructed using acellular dermal matrix. Its incidence, risk factors, pathophysiology, clinical course, management, and long-term sequelae are largely unknown. We present a review of the available literature on this phenomenon and highlight some opportunities for further research.
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Keywords Red breast syndrome · Breast erythema · Acellular dermal matrix · Breast reconstruction Breast implant

Introduction

Red breast syndrome (RBS) is a recently identified clinical entity characterized by non-infectious erythema associated with the use of acellular dermal matrix (ADM) after post-mastectomy reconstruction. The term "red breast syndrome" first appeared in the literature in 2010 in a correspondence between Newman et al. [1] and Nahabedian [2]. Since then, a paucity of research has included RBS as an outcome measure but no studies have addressed this phenomenon directly. Little is known regarding its incidence, risk factors, pathophysiology, clinical course, management, and long-term effects. All of these areas merit further scientific study.

Presentation, Diagnosis, and Clinical Course

Newman et al. [1] and Nahabedian [2, 3] commented on their experience with a syndrome of blanching erythema of the reconstructed breast without local signs of infection. Even so, distinguishing RBS from cellulitis remains a diagnostic challenge; the clinical differences may be subtle. The distribution of the erythema found in RBS was described as being localized over areas where the ADM was placed (typically along the inferior breast), and the phenomenon occurs days to weeks following the procedure. The erythema typically resolves within a few weeks or months without treatment. The degree and distribution of ADM incorporation may influence the appearance of the overlying cutaneous erythema [4].

Clinical features of true infection such as pain/tenderness, skin temperature elevation, fever, and induration are absent in RBS. These findings, however, are only variably present in cellulitis and implant infection and the absence of these findings does not definitively exclude infection. The lack of these physical exam findings should be taken within the context of the full clinical picture.

Leukocytosis and elevation of serum markers, such as sedimentation rate and C-reactive protein, may suggest an infectious etiology but they are nonspecific. The use of procalcitonin levels is an area of ongoing research by other

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specialties in distinguishing true infection from an inflammatory state. Procalcitonin levels have been used to differentiate septic from non-septic arthritis in the rheumatology literature [5]. A randomized control trial demonstrated that procalcitonin-based decision making in patients with viral versus bacterial respiratory infections may decrease the use of unnecessary antibiotics [6]. In contrast, another study found that procalcitonin was not useful in differentiating inflammatory states from bacterial infections in patients with kidney disease [7]. An in-depth review of the literature behind the use of procalcitonin is beyond the scope of this report; however, the results of these studies are promising. Further study may ultimately suggest procalcitonin to be a useful diagnostic adjunct in differentiating RBS from cellulitis, and possibly in other plastic surgery patients where a diagnostic quandary exists.

The long-term sequelae of RBS remain to be seen. With respect to its recent emergence in the literature and recognition as a distinct clinical entity, RBS is still in its infancy and its natural history is uncharted. Although they did not report on the incidence of RBS in their metanalysis, Kim et al. [8] commented that the inflammation may contribute to the often quoted increased rate of seroma formation seen with ADM. The incidence of other long-term complications, such as capsular contracture, RBS recurrence, anaplastic large cell lymphoma, and breast cancer recurrence, is unknown and long-term observation of this cohort of patients is warranted.

Incidence

The true incidence of RBS is yet unknown since many (or perhaps the majority) of these patients may be presumed to have infections and managed as such. Nahabedian [3] estimated an incidence of less than 10 % nationwide and less than 5 % in his experience. Hill et al. [9] reported a 7.6 % incidence of RBS in their study on the risk factors for infection after implant-based reconstruction with ADM. Wu et al. [10] described the effects of tissue expansion on ADM and reported one patient of 31 breast reconstructions (3 %) with RBS. Buseman et al. [11] studied the complications following sterile versus aseptic ADM use in 58 patients for breast reconstruction and reported no patients with RBS (Table 1).

Table 1 Incidence of RBS among studies

	Type of ADM	Patients (*n*)	Incidence of RBS (%)
Buseman et al.	Alloderm, Alloderm RTU	58	0
Hill et al.	NR	65	7.6
Nahabedian	Alloderm	NR	<5[a]
Wu et al.	Alloderm	31	3

RBS red breast syndrome, *NR* not reported

[a] anecdotal

RBS has been described after the use of a variety of different ADM products. It is currently unknown whether there are differences in the rates of RBS among the different ADM products available. Anecdotally, we have noticed a decrease in the incidence of the red breast phenomenon since the incorporation of Alloderm RTU (Alloderm Ready-to-Use; LifeCell, Bridgewater, NJ) into our practice.

Pathophysiology

To date, the etiology of RBS has not been formally studied but was first theorized by Nahabedian [3] to be related to an agent used in the processing of Alloderm (Alloderm; LifeCell, Bridgewater, NJ), and thus he recommended intra-operative rinsing of the product prior to implantation. He reported that biopsy yielded nonspecific findings. Newman et al. [1] observed the RBS with other (unnamed) ADM products and proposed alternative mechanisms, such as lymphatic interruption, histamine release, an immunologic response against the graft, or a vasodilatory response related to vascular ingrowth of the graft. A series of four patients with RBS were described by Ganske et al. [4] in which Veritas (Veritas; Synovis Surgical Innovations, St. Paul, MN) was used in two of these patients, Strattice (LifeCell) in another, and Alloderm in the last. One of these patients underwent punch biopsy of the skin overlying the ADM and also permanent section by pathology when her ADM was ultimately removed. Histology from both specimens demonstrated evidence of a hypersensitivity reaction. In cases where the diagnosis of RBS is clear, surgeons are likely not to risk introducing an infection by obtaining biopsy samples for histology. In more ambiguous presentations, obtaining a biopsy to assist in obtaining a diagnosis may not be useful. These patients are likely to have already been treated with systemic antibiotics and therefore cultures will likely be negative, and any histologic finding may in actuality be a result of the underlying infection or its treatment.

We have observed unilateral RBS in some patients who underwent bilateral reconstruction with ADM at our institution. While this may be related to differences in intra-operative ADM handling (i.e., rinsing) between the two sides, differences in product processing by the manufacturer, or differences in the extirpative procedures, we submit another possible mechanism for RBS that is akin to a local graft-versus-host phenomenon. Whether the pathophysiology of RBS is related to specific product factors, patient factors, operative factors, or a combination of those has yet to be discerned.

Another unanswered question is whether this erythematous phenomenon is seen in other areas of the body where ADM has been employed. ADM has enjoyed widespread acceptance for use by multiple specialties for numerous applications throughout the human body. We speculate that the local tissue reaction in RBS presumably also occurs remotely from the breast at other sites where ADM is used. However, to our knowledge, conditions such as "red abdomen syndrome" or "red lip syndrome" have not been reported. The significance of this observation is unclear.

Prevention and Management

Nahabedian [3] reported that the erythema of RBS is refractory to antibiotic therapy and is caused by substances used in the processing of the product, and thus could be avoided with adequate rinsing of the product prior to use. The senior author (SRJ) routinely rinses Alloderm with one liter of sterile saline followed by immersion of both the ADM and implant in antibiotic solution prior to use. Pre-implantation ADM washing poses no risk to the patient and increases operative time to an infinitesimal degree, while the potential benefit is great.

The erythema should be outlined with a skin marker at the initial presentation to facilitate observation for progression, as was the practice by Newman et al. [1]. In addition to this management strategy, we advocate for sampling of suspicious fluid collections found on ultrasonographic imaging for Gram staining and culture to rule out deep space infection. It is advisable to withhold antibiotics until after any fluid collection is cultured to maximize the chance of identifying an organism in the setting of true infection.

Breast reconstruction patients who develop erythema constitute less than 5 % of all patients at our institution (not published), and likely only a minority of these represents true RBS. We suspect that the vast majority of women who present with erythema have a true soft tissue or implant infection, and therefore our current practice consists of empiric broad-spectrum antibiotic coverage for any post-breast implant patient presenting with erythema. Discontinuation of antibiotic therapy with continued serial assessments is appropriate if infection has been determined to be unlikely. Since the non-infectious erythema of RBS is recalcitrant to antibiotics, it is possible that some of these patients with RBS proceed to operative management, including implant and/or ADM removal, when the concern for infection lingers. Due to clinical ambiguity with cellulitis and other infectious processes, making the diagnosis of RBS may only be possible after a period of close, serial assessments. That is, the diagnosis of RBS may be that of a diagnosis of exclusion or a diagnosis made in retrospection.

Wu et al. [10] identified one case of RBS in their series which was treated with enteral cephalexin and corticosteroids. It is unclear whether corticosteroids hasten resolution of the erythema in this self-limited process. Certainly, corticosteroid use may worsen an unrecognized infection and prolonged corticosteroid use increases the patient's risk for several well-described ill effects. Ganske et al. [4] described one patient who responded to a single course of corticosteroids, one patient treated successfully with corticosteroids who subsequently developed recurrent RBS that resolved with a second course of corticosteroids, one patient successfully treated with montelukast, and another whose erythema resolved on initiation of breast cancer chemotherapy. Our review of the literature neither supports nor disputes the use of corticosteroids, montelukast, and chemotherapy in the management of RBS. The erythema of RBS was described as spontaneously resolving within a few weeks to a few months; the use of corticosteroids may curtail the duration of RBS. The use of anti-histamines has also not been studied. The pharmacological management of RBS, and resultant efficacy, remains a focus of research opportunity.

Conclusions

RBS is a recently recognized phenomenon characterized by non-infectious erythema of a breast reconstructed using ADM. Despite the lack of other clinical indicators of infection and potential role of procalcitonin, distinguishing RBS from cellulitis remains challenging. Furthermore, we suspect that most clinicians would be rightly hesitant to withhold treatment with antibiotics, or even surgical intervention, when confronted by postoperative erythema in the setting of implant-based reconstruction. Unnecessary use of antibiotics encourages the development of resistant microbes and puts the patient at risk for adverse reactions and iatrogenic complications. In contrast, failure to recognize and appropriately treat a true infection may result in great morbidity. Compared to the risk of administering unnecessary antibiotics, the consequences of not treating a true infection are devastating. At this time, we recommend empiric antibiotic coverage upon presentation with prompt discontinuation of antimicrobial therapy if laboratory and imaging studies support a low clinical suspicion of infection. A deeper understanding of the pathophysiology of RBS could decrease the unnecessary use of antibiotics, decrease the rate of unnecessary implant removal, and potentially lead to the discovery of other treatment modalities.

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Conflict of interest All other authors have no conflicts of interest to disclose.

References

1. Newman MI, Hanabergh E, Samson MC (2010) AlloDerm performance in the setting of prosthetic breast surgery, infection, and irradiation. Plast Reconstr Surg 126:1120 (author reply 1120–1121)
2. Nahabedian MY (2010) AlloDerm performance in the setting of prosthetic breast surgery, infection, and irradiation: reply. Plast Reconstr Surg 126:1120–1121
3. Nahabedian MY (2009) AlloDerm performance in the setting of prosthetic breast surgery, infection, and irradiation. Plast Reconstr Surg 124:1743–1753
4. Ganske I, Hoyler M, Fox SE, Morris DJ, Lin SJ, Slavin SA (2014) Delayed hypersensitivity reaction to acellular dermal matrix in breast reconstruction: the red breast syndrome? Ann Plast Surg 73(Suppl 2):S139–S143
5. Shaikh MM, Hermans LE, van Laar JM (2014) Is serum procalcitonin measurement a useful addition to a rheumatologist's repertoire? A review of its diagnostic role in systemic inflammatory diseases and joint infections. Rheumatology. doi:10.1093/rheumatology/keu416
6. Schuetz P, Christ-Crain M, Thomann R et al (2009) Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 302:1059–1066
7. Sitter T, Schmidt M, Schneider S, Schiffl H (2002) Differential diagnosis of bacterial infection and inflammatory response in kidney diseases using procalcitonin. J Nephrol 15:297–301
8. Kim JY, Davila AA, Persing S et al (2012) A meta-analysis of human acellular dermis and submuscular tissue expander breast reconstruction. Plast Reconstr Surg 129:28–41
9. Hill JL, Wong L, Kemper P, Buseman J, Davenport DL, Vasconez HC (2012) Infectious complications associated with the use of acellular dermal matrix in implant-based bilateral breast reconstruction. Ann Plast Surg 68:432–434
10. Wu C, Cipriano J, Osgood G Jr, Tepper D, Siddiqui A (2013) Human acellular dermal matrix (AlloDerm(R)) dimensional changes and stretching in tissue expander/implant breast reconstruction. J Plast Reconstr Aesthet Surg 66:1376–1381
11. Buseman J, Wong L, Kemper P et al (2013) Comparison of sterile versus nonsterile acellular dermal matrices for breast reconstruction. Ann Plast Surg 70:497–499