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Post-acne scarring: A short review of its pathophysiology
[Personal Review]

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Graphics

- Figure 1

SUMMARY

The onset of acne is an expected phenomenon in adolescence. However, its arrival produces long-term psychological and physical sequelae for the individual. A review of available data illustrates the pathophysiological sequence of the advent of post-acne scarring from its humble beginnings as a microscopic comedone to its eventual devastating end point of indented or exophytic scars. Acne scarring shows many different forms and is explainable by the depth and severity of the antecedent inflammation and the ability of the individual to heal these lesions. Post-acne scarring is debilitating and socially disabling for many and is the avoidable outcome of untreated or inadequately treated acne. Treatment will depend on the resultant scar topography.

INTRODUCTION

Acne is a very common disease and has been estimated to affect 95–100% of 16–17-year-old boys and 83–85% of 16–17-year-old girls. 1–4 Acne settles in the vast majority by 23–25 years of age but 1% of males and 5% of females exhibit acne lesions at 40 years of age. 5

There are many factors that influence the onset and extent of acne and the eventual sequela of acne scarring. Acne appears to be hereditary, 6,7 but probably polygenic with variable phenotypic expression. 8 It also is strongly influenced by external factors with diet appearing to be relatively unimportant. 9,10

Acne is highly embarrassing for adolescents, an age with enough of its own intrinsic concerns of self-image. Severe cystic acne causes pain, recurrent bleeding and purulent discharge. In 99% of cases acne affects the face 11 and is associated with poor employment prospects 12,13 and difficulties in interpersonal relationships. 11 Post-acne scarring is particularly devastating and may be a risk factor for suicide. 14

Scarring occurs early in acne and may affect some 95% of patients with this disease and relates to both its severity and delay before treatment. All types of acne, from papulopustular through to nodulocystic disease will scar and adequate treatment must be started early. 15

FROM NORMALITY TO A MICROSCOPIC ACNE LESION

Acne is not primarily a disease of the sebaceous gland nor is it primarily a bacterial infection. It is instead best viewed as an abnormal hyperkeratinization of the follicular epithelium 16,17 with secondary effects on the sebaceous glands aided by the action of Propionebacterium acnes and cellular immunity of the host.

Sebaceous glands

Sebaceous glands occur with greatest density (900 glands/cm^2) in the face, upper neck and chest. 18 Their density on the rest of the body averages less than 100 glands/cm^2.

Sebaceous glands may open directly on to the skin surface without being associated with a hair follicle. These 'free' sebaceous glands are present in the meibomian glands of the eyelid, areolae of the nipples and the glabrous vermilion border of the lip and mouth. 19 These glands are not the sites of acne lesions.

A pilosebaceous follicle is one where a sebaceous gland opens on to a hair follicle and relies on the hair follicle ostium to provide access to the skin surface. These pilosebaceous follicles may be divided up into those with coarse beard hairs with small adjoining sebaceous glands, those with small vellus hairs, with small pores and large sebaceous glands and those with smaller, almost inconsequential, pilary structures and large sebaceous glands. Acne occurs in this last type of pilosebaceous follicle. 20

Androgens produced at puberty and beyond may have a direct role in follicular hyperproliferation, as 5[alpha]-reductase type 1 is present in the infrainfundibular part of the duct as well as the sebaceous gland. 21,22 These rising androgen levels also stimulate mid dermal sebaceous glands to enlarge into large multilobular structures producing large amounts of sebum. The sebum is produced by programmed self-destruction of ripened differentiated and lipid laden sebaceous cells (holocrine secretion) into the sebaceous duct. Patients with acne have a higher sebum excretion rate than non-acne patients. 23,24

This appears important in the pathogenesis of acne with the increased sebum production diluting linoleic acid concentration of sebaceous gland esters. Acne patients have significantly lower skin surface linoleic acid concentrations. 25–27 There is a body of evidence suggesting that such a localized essential fatty acid deficiency of linoleic acid in the sebum bathing the sebaceous follicles may be responsible for follicular hyperkeratinization, which is pivotal in acne formation. 28 Other sebaceous lipids, such as squalene and oleic acid, may have a role in comedogenesis. 29–31

The follicular canal

The follicular canal is composed of two portions, the superficial or upper section, the acroinfundibulum 26 that is structurally similar to the epidermis and contains a stratified epithelium with tonofilaments, desmosomes, keratohyaline granules and melanocytes. 25 The infrainfundibulum is the deeper or lower four-fifths of the follicular canal length and its lining epithelium has a deficient granular layer, fewer melanocytes, desmosomes and tonofilaments but contains numerous lamellar granules. Lamellar granules (Odland bodies) that are plentiful in the normal infrainfundibular wall may act to break intercorneocyte bonds. In a normal follicle, the horny cells are produced but after two or three cell layers these fall apart and are shed into the follicular canal to join the sebum from the sebaceous glands. The earliest event in acne lesion formation appears as a change in this infrainfundibular follicular wall whereby the horny cells become stickier, forming a coherent structure with a prominent granular layer and prominent lipid cellular inclusions. The disappearance of lamellar granules may encourage the impaction of these horny cells leading to dilatation of the sebaceous follicle. At this stage a non-inflammatory microcomedone has been formed. A number of potential fates await this lesion. It may stay as it is, it may enlarge into a closed or open comedone or it may go on to an inflamed acne lesion, be it a papule, pustule, nodule or cyst from which scarring is likely. It has recently been suggested that comedones may cycle explaining why all prone follicles do not exhibit comedo behaviour at the one time and why blackheads and whiteheads clear without treatment being delivered. 20

FATE OF A MICROSCOPIC ACNE LESION

Non-inflammatory lesions: Open and closed comedones

As the impacted keratin expands, compressing and thinning the follicular wall, two non-inflammatory

consequences may occur depending on what happens at the region of the acroinfundibulum. Closed comedones will occur if the acroinfundibulum stays opposed, the pore remaining closed while impacted keratin produces a bulging rounded whitehead or closed comedone below (Fig. 1). Alternatively, the impacted keratinous mass may encroach on the acroinfundibulum, becoming shallower and forcing a dilatation of the pore. The open comedone is thus formed and over the course of time will become wider and darker as melanin granules accumulate from the surrounding acroinfundibular melanocytes. These melanocytes are not active in the infrainfundibulum so closed comedones do not develop this same dark colouring. The sebaceous glands undergo substantial atrophy and de-differentiate as the comedo increases in size. These non-inflammatory comedones do not often produce scarring, as the changes residing within the follicle do not initiate dermal inflammatory and repair mechanisms. When inflammatory changes occur and involve extrafollicular structures with cycles of damage and repair, scarring is a common outcome.

Graphic
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Figure 1 Histology of a closed comedone with impacted keratin and cellular debris within the infundibulum (H&E).

THE CHANGE FROM NON-INFLAMMATORY COMEDONES TO INFLAMMATORY ACNE

Open comedones rarely transform into inflammatory acne. The comedone may expand to several millimetres and some debris is extruded from the surface to the skin surface over time. Through these mechanisms, there is ability for the comedone to deal with any pressure effects of the continuing production of follicular horny cells. These comedones also have duct like comedones within them in communication with sebaceous glands and are able to transfer sebum to the surface. 26

Closed comedones are the site of future inflammatory acne lesions with these lesions being termed ‘time bombs’. 32 A mixed morphologic and aetiological classification has been proposed. Comedones divided into microcomedones, ordinary comedones, missed comedones (visible only on stretching of the skin), sandpaper comedones particularly seen on the forehead, submarine comedones (large missed ones), large (macrocomedones) or grouped large comedones (conglobate), drug induced and naevoid comedones. 20 This classification may have therapeutic implications.

In the largely anaerobic conditions existing in the impacted milieu of the closed comedone P. acnes, an obligate anaerobe flourishes. Although Pityrosporum ovale and Staphylococcus epidermidis are also skin and pilosebaceous duct organisms, it is P. acnes that is important in the pathogenesis of inflammatory acne. 33 Comedone formation and the initiation of acne proceed quite happily without the involvement of microorganisms. Propionebacterium acnes is involved in the conversion of non-inflammatory comedonal acne to inflammatory acne, with the consequent risk of scarring.

Inflammation in acne is a two-stage process with lymphocytes and neutrophils affecting the attenuated follicular wall of the closed comedone (Fig. 2) and, if this wall is breached, the extravasation of irritating follicular contents into the dermis leads to a variety of lesions. 25 The search for the cause of the breach of the follicular wall has been a long one. Initially it was blamed on the free fatty acids from hydrolysis of sebaceous gland triglycerides courtesy of the lipases liberated by P. acnes. 34,35 These are irritating substances 36 that are hypothesized to allow penetration of the follicular wall. It is, however, doubtful that physiologically there is enough production of free fatty acids to exert this inflammatory effect. 37 However, these free fatty acids liberated in follicles colonized by P. acnes may be able to entice comedogenesis, although as discussed above, they are not essential for this comedogenesis to occur. 38 However, P. acnes is important in generating inflammation, with ability to chemoattract polymorphonuclear leukocytes by the liberation of a low molecular weight chemotactic substance. 39,40 This substance is presumed to be diffusible through intact follicular walls and to be responsible for the intrafollicular location of leucocytes. 41 The

neutrophils ingest the offending P. acnes with release of intracellular hydrolytic enzymes, but do not appear to kill the bacteria. 42 There have also been antibodies found to P. acnes 43 in microcomedones and interaction with these antibodies may liberate hydrolytic proteases that weaken the follicular wall and allow extrusion of irritating intrafollicular contents into the dermis. 25

Graphic
[Help with image viewing]

Figure 2 Histology of a comedone containing acute inflammatory cells (H&E).

FOLLICULAR EXPLOSION: THE ONSET OF DERMAL INFLAMMATORY DISEASE

Hairs, lipids, keratin, bacteria and effete cornified cells excite foreign body inflammation as they enter the dermis from the burst follicle. Ingestion of bacteria and other structures occurs but with incomplete intracellular digestion and destruction of these structures. The consequence of this is for many neutrophils to succumb, liberating both the incompletely dealt with P. acnes and neutrophil intracellular enzymes 44 into the extracellular dermal environment. The released P. acnes activate both classic and alternative complement pathways including C5a neutrophil chemotactic factor dragging in more neutrophils to amplify the inflammatory response. 45 The free fatty acids initially produced by the intrafollicular lipase activity of P. acnes are also now in the dermis and are irritating to their new environment. 46

The severity of inflammation in acne has been linked to antibody titre to P. acnes. 47,48 Those unfortunate patients with severe inflammatory acne appear to have elevated indices of lymphocyte transformation to P. acnes antigens, 49 abnormal neutrophil chemotaxis and phagocytosis 50 and excess activation of macrophages. There is considerable evidence against P. acnes causing actual dermal infection, as they tend to perish rapidly in human tissue. 25 It also seems to be unimportant whether the organisms are alive or dead in terms of their ability to incite an inflammatory response. 25,51 Thus the role of P. acnes is to incite the breach in the follicular wall and to be part of the chemotactic and proinflammatory cascade that follows.

THE EVOLUTION OF INFLAMMATORY LESION TO SCAR FORMATION

The end result of follicular rupture is a perifollicular abscess. Small abscesses incorporating the horny core will point and be discharged through the skin. This will be repaired without scarring in about 7–10 days. The epidermis is always attempting repair and cells grow from the epidermis and appendageal structures to encapsulate the inflammatory reaction. If this is complete, there is resolution of the lesion without incident. Sometimes, however, this encapsulation is incomplete and further rupture occurs, the end result may be the appearance of multichannelled fistulous tracts. 26,52 This may appear as grouped open comedones with histologically a number of interconnecting keratinized channels being seen. These fistulas may be so large that a bridge of normal tissue is clearly visible overlying a tunnel of scar tissue. Ice pick scars are also of this variety with histology showing these to be reticulate tunnels lined by hyperplastic epithelium. Often there are remnants of inflammation even in old scars of this type.

Other types of outcomes depend on the extent and the depth of the inflammation. If the dermal inflammation is severe, total necrosis of the follicle may ensue and sloughing will produce a focal scar.

If the inflammation is severe and especially if rupture occurs deeply in the follicle the inflammation will extend well beyond the environment of the hair follicle into the subcutis, along vascular channels and around sweat glands. 26 This wreaks havoc in these deep tissues inducing deep scarring and destruction of subcutaneous fat.

The inflammation is very deep and transepidermal discharge is often not available as a method of resolving the abscess. As healing occurs, attempts at encapsulation of this deep inflammation ensue. This may form into

papules, nodules or cysts. Cysts are in effect giant closed comedones (Fig. 3).

Graphic
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Figure 3 Histology illustrating cystic change within an inflamed hair follicle (H&E).

The outcome of inflammation and scarring is either an atrophic or a hyperplastic response.

The nature of acne scarring

Acne scarring will be obvious if it exhibits certain characteristics especially those of contour and colour. Contour abnormality, in particular, is not tolerated well visually. Acne scarring is most often a contour problem being one of excess (hypertrophy) or of loss (atrophy) of tissues. In addition, scars may be obvious because of their red, white or brown colour. Scarring is also obvious if it distorts free margins, crosses over cosmetic boundaries or is longer than about a centimetre. Acne scarring most often is atrophic and shows many grades of severity.

Atrophic acne scarring

Atrophy may affect both dermis and subcutis. Inflammatory acne lesions are like all healing scars maturing through the phases of healing from initial inflammation and granulation tissue formation to subsequent fibroplasia, neovascularization, wound contracture and tissue remodelling.

However, acne lesions are unusual in that the inflammation is initiated beneath the epidermis in the infrainfundibular region of the pilosebaceous structure. 53 Thus the subsequent scarring often involves deeper structures rather than just the surface. As the scars ultimately mature, their contraction draws in these surface layers leading to an indented appearance. The enzymatic activity and inflammatory mediators also destroy the deeper structures and this loss of structure contributes to the severity of atrophic scarring (Fig. 4).

Graphic
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Figure 4 Histology showing scar tissue with some in-drawing of the surface epithelium (H&E).

Types of atrophic scars

The depth and the extent of the inflammation will determine the amount, type and depth of scarring (Fig. 5).

Graphic
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Figure 5 Atrophic acne scarring.

Superficial macular scars

If only the epidermis and superficial dermis are involved the scars may appear as macules that may be discoloured either erythematous if inflamed and comparatively early or young scars (under 1 year) or with altered pigmentation (Fig. 6). Pigmentation may be increased in more olive skin patients and represents mostly post-inflammatory hyperpigmentation that will fade in 3–18 months if sun protected. Reparative treatment may not always be required. If treatment is sought, medical therapy may suffice with topical

reparative creams such as retinoic acid or [alpha]–hydroxy acids often used in conjunction with topical corticosteroids. Alternatively or additionally, light skin peels with glycolic acid or Jessner's solution or variants may be utilized. Occasionally vascular or pigmented lesion lasers or light sources may be useful for resistant cases. 54 Hypopigmented or depigmented macular acne scars are a relatively common end point of long-standing acne and are very difficult to treat.

Graphic
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Figure 6 Superficial macular scars.

Deeper dermal scarring

In an often unfortunate attempt at repair, sheaths of cells grow out from the epidermis and appendageal structures. This encapsulation of the inflamed contents may be completely or partially effective. If this encapsulation is only partially effective recurrent rupture of the follicle may ensue and multichannelled tracts eventuate (Fig. 7). 52 In such circumstances, excision of the entire multichannelled apparatus may be required. However, this is often difficult as any persistent sinus tract left behind will become an inflammatory nidus or cyst and there may be transepidermal elimination of this inflammation. This may give the appearance of infection in the excision line but represents only the body's attempt at exteriorization of deeper cystic contents.

Graphic
[Help with image viewing]

Figure 7 Multi-channelled sinus tracts with paper clip under bridging scar.

If the deeper dermis is affected in a punctate fashion, sharp walled or ‘ice pick’ scars are produced (Fig. 8). These are resistant to most corrective techniques and require punch techniques for satisfactory resolution.

Graphic
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Figure 8 Ice pick scars in a field of multichannelled scars on the cheek.

If there is more extensive dermal damage, linear or broader troughed scars may result. It is important to conceptualize where in the skin the scar is occurring from its appearance. A well-defined linear troughed scar is a dermal event and will benefit from dermal augmentation (Fig. 9). A large, deep ill-defined defect is not predominantly a dermal event but is deeper and needs subcutaneous augmentation.

Graphic
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Figure 9 Linear dermal scar.

Perifollicular scarring

Follicular or perifollicular acne inflammation produces hypopigmented papular scars from destruction and attenuation of collagen and elastin fibres in the surrounding tissues around the hair follicles. This is most common on the trunk 55 and is largely untreatable.

Fat atrophy

The inflammatory mediators present in the deep cystic acne lesions destroy facial fat. The cystic lesions are also space occupying and their eventual involution will leave a void that cannot be filled by the atrophied subcutaneous tissues. Instead the tissues are drawn in from surface layers and this effect is worsened by the contracture of the scarring around these cysts. This cystic involution and maturation probably explains the incongruous worsening of a patient's appearance that is occasionally seen after cystic acne is brought under control especially by isotretinoin.

Lipoatrophy occurs in a general way as a result of the ageing process. The sharpness of the convexities of the cheeks, chin and frontal bossing diminish and the concavities of the pre-auricular, temples, inframalar and perioral tissues become exaggerated (Fig. 10). There is a compartmentalization of the face that is not seen in youth and this largely represents subcutaneous tissue changes. Concavities thus created tend to exaggerate the appearance of facial scarring with scars tending to drop into these structurally deficient zones. If the destruction of fat by deep inflammation occurs in these relatively fat deficient areas then the scarring will appear to be particularly severe and will become worse as the patient ages.

Graphic
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Figure 10 Ageing changes of fat atrophy superimposed on old acne scarring.

CONCLUSION

The microscopic closed comedone is not a disease but its sequela, the acne pustule, may develop into a devastating one, destroying the well-being and self-esteem of the individual. It may have many outcomes, depending on the degree and depth of inflammation, as well as the efficiency of the host response to this inflammation.

Treatment for acne should be early and aggressive to avoid scarring which is an early and permanent outcome of inadequate treatment. Treatment of acne scarring is much more tedious and ineffective than its prevention.

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