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Case Report

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Very Severe (4th Grade) Closed Comedonal Acne Vulgaris That was Complicated by Staphylococcus Epidermidis and Pityrosporum Ovale Folliculities in 16th Years Old Atopic Hystory Girl that was Treated with 4x Tca 10% Chemical Peeling at 2 Weeks Intervals

Lely Nurjanti

Dermatoveneorologist Samarinda East Kalimantan Indonesia

***Corresponding author**
Lely Nurjanti, Dermatoveneorologist, Samarinda East Kalimantan, Indonesia.
E-mail: lelynurjanti@yahoo.com

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Abstract

Acne vulgaris was very common self limitting disease, affected approximately 85% of adolesence, that was defined as a chronic inflammation of pilosebaceous units. It was characterized (diagnosed) by the formation of comedones (as primarily acne lession), erythemathous papules and pustules, less frequently nodules and pseudocyst, and was accompanied by scarring in some cases that caused psychosocial problems. Cunliffe classified the severity of acne vulgaris into 4 types based on the kind and number of acne lessions : mild, moderate, severe, very severe. Four major factors were involved in the etiopathogenesis: follicular hyperkeratinization, increased sebum production, abnormality of microbial flora and inflammation process. The goal of therapy were : removed plugging of the pilar drainage, reduced sebum production, treated bacterial colonization, prevented from scaring. The complications were acne scar, persistent hyperpigmentation, pyogenic granuloma formation, persistent swelling, gram negative bacteria folliculitis, bacterial and fungal folliculitis as secondary infection, resistances to antibiotics.

The purpose of this case report was to share experience in treating very severe comedonal acne vulgaris because of the chronicity course of acne vulgaris was difficult to be eradicated and there were many resistances problems to antibiotics in some literatures and journals.

***Case Presentation:** It was a very severe (4th grade) closed comedonal acne vulgaris that was complicated by Staphylococcus epidermidis and Pityrosporum ovale folliculitis in 16th years old atopic hystory girl based on anamnesis, clinical finding and laboratory examination. And this case was treated by 4x TCA 10% chemical peeling at 2 weeks intervals, 2 weeks antibiotic and 10 days ketokonazole after the result of culture and laboratory examination were positive. And the result was good. There was significant improvement in clinical stage (4th grade to 1st grade acne vulgaris), decreased the count of comedones, diminished papules-pustules and inflammation, no scar and post inflamatory hyperpigmentation were occured*

***Discussion:** TCA 10% was superficial chemical peeling, considered as adjunctive therapy to the first line acne therapy retinoids and antibiotic, and TCA was the first line therapy for acne scar and skin rejuvenation. TCA was cheap and save because no systemic absorbtion, had keratolytic effect (comedolytic action) and anti inflammatory effect (bactericidal action). It could be combined to antibiotics and antifungal therapy and solved resistance problems to antibiotic and antifungal in acne therapy.*

Keywords: Acne Vulgaris, Etiopathogenesis, Tca Chemical Peeling

Introduction

Definition

Acne vulgaris was a very common self limitting disease, that was seen primarily in adolescent. It was defined as a chronic inflammation of the pilosebaceous units [1-4]. Acne was not infectious [3].

Incidence

Acne vulgaris affected approximately 85% of young people [1,3,4]. The age of onset was at puberty, typically 12-15 years, but could firstly appeared at 25 years old [1,4]. the peak insidence of acne vulgaris was in 17-21 years (17-18 years in female and 19-21 years in males) [4]. Acne vulgaris was more severe in males than females [1]. The lower incidence of acne vulgaris was in Asians and Africans [1]. Acne in Black Americans were less evident than white Americans [3].

Diagnosis & clinical manifestation

Acne vulgaris was characterized (diagnosed) by the formation of comedones (open/black head and closed/white head), erythemathous papules and pustules, less frequently nodules and pseudocysts (could

been ruptured, reencapsulated, inflammed and formed abscesses), draining sinus tracts (round isolated single nodules and cysts coalesce to linear mounds), that was accompanied by scarring in some cases [3]. Acne vulgaris lessions were polymorphic due to inflammation process of acne lessions [4]. Comedones were the primarily lessions of acne, but they were not unique and could been found in other skin disease like senilis comedo [1]. The predilection of acne vulgaris were on the face, trunk, upper arms and buttock [1]. Seborrhea of the face and scalp frequently presented and could been severe [1].

Duration of lession: The duration of lession was weeks to months [1].
Season: Acne vulgaris was worsen at winter and fall [1].

Symptom

It was Itchy and pain especially in nodulocystic type [1]. Itchy was rare. It could been found in early phase of acne or in succesfully treatment cases. Itchy was caused by releasing histamine like substances that were produced by *P acnes* that were killed by treatment [4]. Pain was also rare, could been found in patients with nodule and sinus espescially on the trunk [4].

Classification

Fitzpatrick classified acne vulgaris as non inflammatory lessions (white head and black head comedos) and inflammatory lession (papules, pustules, nodules, cysts) [1]. Plewig and Kligman in 1975 classified acne vulgaris in 3 types : comedonal, papulopustular and conglobata [5]. Cunliffe classified the severity of acne vulgaris according to the number and types/kinds of the lession into 4 types of acne vulgaris : mild, moderate, severe and very severe acne vulgaris [4]. The types of lession were: comedones, papules/pustules, nodules/cysts/sinus tracts, inflammation and scarring [4]. This case report classified and judged the severity and after treatment clinical improvement of acne vulgaris based on Cunliffe classification criteria.

Laboratory Examinatio

No laboratory examination were required [1]. In the majority of acne patients had normal hormonal levels [1]. If endocrine disorders were suspected (especially in patients who had clinical manifestation of hyperandrogenism like irregular menses, hirsutism, hoarse voice, alopecia androgenism), determined free testosterone, follicle stimulating hormone, luteinizing hormone and DHEAS to exclude hyperandrogenism and polycystic ovary syndrome [1,3,4]. Recalcitrant acne could also been related to congenital adrenal hyperplasia (11β atau 21β hydroxylase deficiency) [1].

Etiopatogenesis

Acne vulgaris was multifactorial disease of pilosebaceous follicles. The important patophysiology of acne vulgaris were follicular hyperkeratinization, increased sebum production, P acne colonization, Inflammation [1].
Four major factors were involved in the etiopathogenesis [1-4].

1. Follicular hyperkeratinization and cornification of the pilosebaceous duct.

It was not been known whether the initial trigger for acne was seborrhoea or ductal hyperkertanization or both [4].
Several factors that might been important as ductal hypercornification/ follicular hyperkeratinization mechanism were: [1-4].

a. Abnormal response to androgen
b. Abnormal lipid composition of the ductal corneocytes (local deficiency of linoleic acid)
c. Local cytokine activity (IL1α)
d. Microbial factors

Androgen that quantitatively and qualitatively normal in serum stimulated sebaceous glands to produce more sebum, there was high sebum secretion rate [1]. Essential fatty acid linoleic deficiency were characterized by inducing follicular hyperkeratosis, impacting of corneocyte and decreasing epithelial barrier function, low level linoleic acid led comedogenesis [1,3,4]. The changing in sebum secretion or composition (could flourished microorganism growth that activated immune system) could led to release of IL 1α by follicular keratinocytes, which in turn could stimulated comedogenesis [1]. Pro inflamatory cytokine stimulated abnormal keratinocyte proliferation and differentiation revealed obstruction [1,2]. Follicular plugging was formed and would prevented the drainage of sebum and androgens [2]. There was follicle impaction and distention, formed comedos that were disrupted and ruptured, there was leakaged of follicular materials that induced inflammed lessions [2,4].

The early hypercornification of acne was not been initiated by bacteria, but later there were microbacterials grew and bacterial lipases converted triglycerides to free fatty acids, there was changed of sebum composition and diluted linoleic acid concentration that led hypercornification (follicular hyperkeratosis) and comedogenesis [1,4].

Comedones represented as the retention and hyperproliferation of ductal corneocytes in the duct [3,4]. There were accumulation of multiple corneocytes in the duct could been caused by either an increased in production of basal keratinocytes or failured of the keratinocytes to be expelled from the duct [4].

Ductal hypercornification hystopathologically was presented as microcomedones and clinically as blackheads and whiteheads [3]. There was a signifficant correlation between the severity of acne and the number and size of follicular casts in comedogenesis [3]. There was an increasing in proliferation of ductal keratinocytes of non affected and affected follicles. Hystologically microcomedos were found in normal nearby sites of acne and area that was affected with acne [3]. The primary abnormality that led to hypercornification was not been related to change in keratin expression, hypercornification and comedogenesis might been related to failure the ductal corneocytes to separate [3].

The primary changed in the sebaceous follicle in acne was an alteration in the pattern of keratinization within the follicle [1]. Normally keratinous material in the follicle was loosely organized. In ultrastructural level, there were many lamellar granules and relatively few keratohyaline granules. Comedo formation was firstly formed in the lower portion of follicular infundibulum (infrainfundibulum) [1]. The keratinous materials were denser, the lamellar granules were less numerous, keratohyalin granules were increasing and some of cells were containing amorphous materials (which were probably lipid). were generated during the process of keratinization [1]. Kinetic studies demonstrated that there was an increasing in cellular turn over in comedones [1].

Corneocytes frequently contained about 20 % water but they were

varies markedly with age [4]. The swelling of the epidermis was caused by hydration, that followed prolong soaking of the skin, particularly in warm water, was familiar in most people. Corniffied epithelium of the sebaceous follicle became hydrated, that might increased sebum outflow resistance by reducing the size of the pilosebaceous ostium [4]. This obstruction was associated with a decreased in outflow of sebum [3]. Acute obstruction of a particular pilosebaceous duct might then occured and thus precipitated acne [4]. It explained tropical acne and pre menstrual acne flared [3].

Comedogenesis was also related to the potential importance of what was called the sebolemmal sheath [3]. It had been suggested that the excretion of products from the sebaceous gland was occured through an organized acellular tubular conduit-the sebolemmal sheath was produced by sebaceous duct cells. The rupture of this sheath might contributed to comedogenesis [3].

a. Abnormal response to androgen influenced hypercornification

The evidence was accumulating to propose that androgens (a male steroid hormone such as testosterone) might play an important role in comedogenesis [3]. The cells of pilosebaceous duct had androgen receptors and 5α reductase type I (enzym that converted testosterone to DHT) was also present in this cells [3].

Androgen were known to regulate the development of sebaceous gland and sebum production. Androgen might played indirect at the follicular hyperkeratinization was supported by some obsevations [1].

1. Androgen receptors had been localized to the outer root sheath of the infrainfundibular region in the follicles.
2. The formation of follicular cast reduced in patients that was treated with anti androgen.
3. Each of the key enzyme involved in androgen metabolism had been identified in the follicles.

b. Abnormal lipid composition in keratinocyter duct influenced hypercornification

Follicular hyperkeratinization might related to a local deficiency of linoleic acid, production of IL 1α within the follicle or possibilly the effect of androgens (high sebum secretion rate) [1]. Low essential fatty acid linoleic caused :

- ✓ Inducing follicular hyperkeratosis/hypercornification (which might parallel with the increased scale that was found in comedo) [1,3].
- ✓ Impacting of corneocytes that formed comedones [4].
- ✓ Decreasing epithelial barier function1,3 (which might made the comedonal wall more permeable to inflammatory substances) [1,3,4].

Membrane coated granules were probably more related to barrier permeability than cell separation and that were decreased in commedones [3]. In examination of polar lipids recovered from comedone showed that the acyl ceramides were contain only 6% linoleic acid among esterified fatty acids, compared with 45% in normal human epidermis[3]. Linoleic acid concentration was decreased in acne patients sebum [3].

Other lipids had been incriminated, there were free fatty acids, squalene, squalene peroxides, oleic acid, isopropyl niristate, liquid parafin, wax ester, ceramid, linoleic acid. Low ceramides and low level linoleic acid essential fatty acid in ceramide had been blamed for inducing comedones [3,4]. There were correlation between lipid peroxidase levels (an oxidative degradation of lipids resulting in cell damage) and the size of comedos. There were low level of linoleic acid and high sebum level in acne patients [4]. UVA radiation in lipid substance composition (squalene, oleic acid, isopropyl nyristate, liquid paraffin) induced comedogenesis [4]. There was high sebum flowed that produced a local deficiency of vitamin A in the duct that induced ductal cornification [4]. Than the changing in sebum secretion or composition could led to release of IL 1α by follicular keratinocytes, which in turn could stimulated comedogenesis [1].

The primary site of the developing comedone in the sebaceous follicle in acne vulgaris was at the level of the infrainfundibulum [4]. It was proposed that at the time of cell division, when the sebaceous cells still had an contact with the basement membrane, they still had and access to circulating lipid, including linoleat [4]. Once sebum synthesis began, no further lipids were accepted from circulation, so that more sebum was synthezised per cell, and linoleate content would been diluted [4]. This linoleate content would been released at the time of final cell ruptured and incorporated into various lipids in proportion to be relative rates (linoleic acid was diluted by sebum and the concentration would been low), at which these lipids were being synthesized at the time of cell ruptured [4]. Linoleic acid was essential fatty acid that could not been synthesized by human cell tissue [3,4].

The pilosebaceous unit comprised an matured epiuthelium and developed sebocytes through which the hair and sebum passed. Anatomically the pilosebaceous unit was divided into smaller units infundibulum (acroinfundibulum and infrainfundibulum) and sebaceous duct [4]. The sebocytes rest on the basement membrane that were contiguous with the dermis and extending from this basal layer into the central part of the gland. The sebaceous gland was a holocrine gland, the secretion was the result of self destruction of the sebocytes. The nucleus was moved to the periphery of the cell. The cell then entered the pilosebaceous duct. The sebum was secreted, than it was moved up with desquamated corneocytes and presented microbes to the surface [4].

c. Local cytokine influenced comedo formation

Inteleukine 1α was found in comedo, it was important in comedogenesis and it was produced by keratinocytes of the duct [3]. It was proved by in vitro study. This effect could been blocked by Interleukine 1 antagonists and the formation was totally disrupted by EGF (Epidermal Growth Factor) [3,4].

d. Microbial factors influenced duct hypercornification

Two studies had failed to incriminate bacteria in the initiation of comedones, and it was proved by the fact that there were no bacterias that had been shown in some early comedones. Ultrastructurally and cultures of some early non inflamed biopsy material that were taken from lessions were sterile [3,4].

PP. acnes was not involved in the initiation of comedones but might been involved in the later stages of comedogenesis [3,4]. The early hypercornification of acne was not been initiated by bacteria, but later there were bacterias colonization that produced lipase that converted triglyserida to free fatty acid, and increasing sebaceous free fatty acids would been changed sebum composition and diluted linoleic acid concentration that led hypercornification (follicular

hyperkeratosis), corneocytes impaction that formed comedo4 and decreasing epithelial barier function that increased permeability of comedonal wall [1-4].

Biopsy and culture of early non inflammed lessions had shown that 30% of these were without bacteria suggesting that ductal bacteria were not needed for initiation of cornification [3]. Electron microscopy of early non inflammed lessions that were taken from prepubertal and early pubertal individual had demonstrated few or no bacteria [3]. Quantification of bacteria from comedones suggested that follicular colonization might been unrelated to comedogenesis [3].

2. Increased sebum production.

Normal or abnormal androgens stimulated sebaceous glands to produce more sebum or there was end organ androgen hypersensitivity response in normal hormonal level of acne vulgaris that made bacterial and fungal were flourished [1,3,4].

There was much debated concerning the prime trigger to acne, it was the increased of sebum production or formation of comedones or both abnormality developed paralel in the same acne prone pilosebaceous follicle [4]. Lipid composition influenced comedones formation [4].

Sebum excretion increased in acne patient than normal people and the increasing of sebum exctretion was equally with acne severity [3].
Increased production of sebum in acne patients was explained as 4 possibilities [4]:

1. An elevated level of circulating hormone that was caused by an abnormal pituitary drive
2. An abnormal increase in the production of androgen in the adrenal and gonad,
3. An end organ hyper response of the sebaceous glands to normal circulating level of hormone.
4. Combination

In most of acne patients had no hormonal misfit. Most patients in clinic did not require investigations of sex hormones simply because the patients seem otherwise normal, they responded well to an appropriate treatment reasonablly and thus did not need detailed endocrinological examination [4]. There was rare cases that acne female patients had clinical sign of abnormal hormonal level like excessively hairy, hoarse voice, irregular menses and they got on well with the men and could been pregnant. In this patient could been found an elevation levels of circulating androgens or an abnormal pituitary drive [4].

There was an end organ hyper response of the pilosebaceous unit to normal levels of circulating androgens. And it was supported by the finding that the sebaceous glands in acne prone areas function differently to those in non prone areas, so acne could been found only on the trunk and none on the face, or acne just on the face and none on the back and chest [4].

A connection between acne and high rates of sebum secretion was supported by at least 3 types of evidence[1] :

1. Children did not get acne during the age range from approximately 2-6 years, when sebum secretion was extremely low.
2. Average rates of sebum secretion were higher in individuals with acne than those without acne.
3. Treatment that reduced sebum secretion (such as estrogen, 13 cis retinoic acid) improved acne.

Increased sebum production was presented as patient`s seborrhoea (greasy skin) [3]. Active sebaceous glands were a prerequisite for the development of acne. Acne patients male and female, excreted on average more sebum than normal subjects, and the level of sebum secretion correlated reasonably well with the severity of the acne [3]. Sebaceous activity was predominantly dependent on androgens sex hormones of gonadal or adrenal origin [3]. Abnormally high levels of sebum secretion could been thus resulted from high overall androgen production or increased availability of free androgen, because of a deficiency in sex hormone binding globulin (SHBG) [3]. Equally they could involved an amplified target response mediated either through 5α reductase of testosterone or an increased capacity of the intracelluler receptor to bind the hormone [3].

Lawrence et al found that only 41% of the acne patients had free testosterone level above normal. Lucky et al measured a number of androgens and their precursors as well as, and found that 52% of non hirsute women with acne had at least one abnormal hormone level. Darley et al found high sebum testosterone in 26%, low SHBG in 45% and high prolactin in 45% of 38 woman with acne However 24% of the total had no hormonal abnormallity [3]. Peripheral androgen metabolism might been important for example increased androsterone metabolism had also been reported in normo androgenic females [3].

In some published papers, it would seem that androgenic hormonal balance was disturbed in 50-75% of female acne patients [3]. However, this had not been established that it was the critical factor, and at least a quarter of all cases remain unexplained [3]. The development of acne were simply related to systemic hormone levels. But in general, acne patient had not frequently had endocrine misfit [3].

The acne did not occur simultaneously on all susceptible sites was consonant with the finding that sebum secretion were varies from follicle to follicle. In acne patients, there were marked heterogenicity in individual follicular sebum excretion [3]. This suggested that certain follicles might been proned to acne. An enhanced peripheral response should been considered as a factor in many subjects [3].

The possible role of increased 5α reductase of testosterone to its more active metabolite was indicated, both by the deminstration that sebaceous glands in acne prone regions showed abnormallity high 5α reductase activity in vitro, and by the finding of abnormally high ammount of 5 alfa androstenediols in the urine of female acne patients [3]. There were 2 forms of 5α reductase, type I and type II, and the type I 5α reductase was more relevant. The activity of type I 5α reductase in isolated sebaceous glands also supported the end organ hyperresponsiveness theory for acne [3]. Androgen action on the sebaceous gland might been independent from serum hormone levels [3].

There was possibility that other hormones affected the sebaceous glands, either directly or by enhancing their response to androgens [3]. Low sebum excretion rate was low in individuals with isolated growth hormone deficiency, but this endocrinopathies was rare [3].

Sebum consisted of mixture of squalene, wax and sterol esters, cholesterol, polar lipid and triglyserides. As the sebum moved up the duct, bacteria especially *P acnes* hydrolized the triglycerides to free fatty acids, which eventually appeared at the skin surface. Free fatty acid fraction of the sebum was considered to be important in the causation of inflammation [1,3]. Triglycerides fraction in sebum was probably responsible for acne [1].

The role of individual lipid components in causing acne was uncertain. Lipid might been involved in ductal hypercornification or might been essential to the growth of bacteria [3]. Sampling of skin surface lipids had shown that patients with acne tended to have higher levels of squalene and wax esters, and lower levels of essential fatty acids linoleic acid, and a more frequent occurences of particular free fatty acids [3]. Linoleic acid was significantly reduced in ductal hypercornifications [3]. Linoleic acid levels were signifantly decreased in acne patients and there was inverse relationship between sebum secretion and linoleic acid esential fatty acid concentration of sebum [1]. Linoleic acid could not been synthesized in mammalian tissue and its concentration was diluted by subsequent endogenous lipid synthesis in sebaceous cell [1].

In was unclear, why elevated rates of sebum secretion led to acne. The triglyceride fraction of sebum, which was unique to humans, was probably responsible for acne. The bacterial population of the follicle hydrolized triglycerides to fatty acids, which eventually appeared on the skin surface. In the past, the free fatty acid fraction of sebum was considered to be important in the causation of inflammation, but in recent years it had become evident that there were probably other more important causes of inflammation [1].

The sebaceous glands produced a considerable amount of sebum in the first 3 months of life, which then gradually reduced to zero at 6 months of age. This neonatal stimulus was likely to be an effect of the fetal and neonatal adrenal androgens. After 6 months of age the sebaceous gkands remained quiscent until early adrenarche. At adrenarche, around 7-8 years, there was an increased in adrenal androgens, in particular dehydroepiandrostenedione, with the resultant increased in sebum excretion. In the early pubertal years there was a further increased in adrenal androgens and gonadal androgen stimulus to the sebaceous gland. There was an obvious increased in greasiness of the skin (seborrhoea), even in subjects who did not have acne. The sebaceous gland was under endocrine control. The main stimulus to the sebaceous glands was androgens. The pituitary had an important role in controlling the androgen production via the adrenals and gonads. The adrenals in particular produced dihydroepiandrostenedione and the gonads in both sexes produced testosterone. The circulating androgens, in particular testosterone were bound to the sex hormone binding globulin and it was the 1-2% of free testosterone was dictated sebaceous gland activity [4].

In both sexes, independent of the presence or absence of acne, there was a gradual increased in sebum excretion from puberty and beyond reaching a peak at about the age of 16-20 years. Thereafter the level remained constant until there was a gradual decreased from about 40 years onwards in women and from about 50 years in males. In general, the sebum exretion rate (SER) in men was signifficantly higher than in women [4].

Patients with acne also had seborrhoea indeed many patients complained that as acne developed so there was an increased greasiness of the skin and on the scalp. There was a reasonable correlation between the amount of sebum production and the severity of acne. There was an evidence that those subjects with seborrhoea and acne had a higher number of sebaceous lobules per gland. Indeed one of the disappointing features of acne therapy with most therapies were the fact that despite an improvement in the acne the sebaceous was persisted. But in Dianette (cyproterone acetatate+ethinyl estradiols) and isotretinoin therapy, there was a significant reduction in sebum excretion and acne improvement [4].

Measurements of sebum excretion also showed that individuals with acne produced more sebum than individuals who had never had acne. There was a gradual decreased in sebum excretion beyond the age of about 40 years. Thus reduction in sebum alone was not accounted for resolution of acne [4].

There were differences of the lipid composition between the skin surfaces and in the sebaceous glands. Skin surface lipid composition had less triglycerides and more free fatty acids levels, and equally same levels of wax esther, squalene, cholesterol esters and cholesterol. It was caused by lipolityc enzymes that were produced predominantly by *P acnes* and *Staphylococcus epidermidis* that hydrolized triglycerides into free fatty acids when the sebum was moved up from the pilosebaceous duct [4].

3. The abnormality of the microbial flora.

Bacterial and *Pityrosporum ovale* `s lipase hydrolyzed triglycerides to free fatty acids that flourished bacterials and *Pityrosporum ovales* themselves [4]. There was lipid composition changing and free fatty acid would marked inflammation process [3,4]. Free fatty acid was comedogenic [4]. Bacterial and fungi were bound to the receptor of monocytes, keratinocytes, perifollicular and peribulbar macrophages, sebocytes, langerhans cells and other inflammatory cells (through TLR2 Receptor or others) and T lymphocytes (through CD4) than produced proinflammatory mediators (IL1α, TNFα, etc) that led to an inflammatory response [1,3,4,6]. *P acnes* induced TLR 2 Receptor expresion and play role in acne inflammation [6].

Adolescence and its attendance seborrhoea were associated with a significant increased in *P acnes* [3]. But there was a little or no relationship between the number of bacterias on the skin surface or in the duct with the severity of acne [3]. But in other books Cunliffe said that there was a correlation between the reduction in *P acnes* counts and the clinical manifestation of acne [4]. The development of resistance to *P acnes* might equated with clinical failure to treat the acne [4]. There was no *P acnes* colonization in non acne vulgaris patients [3]. *P acnes* colonization were at anterior nares [4]. And *P acnes* were important in acne pathogenesis [1].

Sebum excretion rate and ductal cornification correlated well with clinical severity [3]. Acne was not infectious [3]. TThe three major organisms were isolated from the surface of the skin and the duct of patients with acne were *Propinibacterium acnes*, Staphylococcus epidermidis and *Malassezia furfur/Pityrosporum ovale* [3]. There were three major subgroups of the propionibacterias : *P acnes*, *P granulosum* and *P avidum* [3]. Almost certainly *P acnes* and to lesser extended *P granulosum* were the most important [3]. Nevertheless, as they lived in association with the *Staphylococcus epidermidis* and *Malassezia furfur*, three organisms had probably some control over the growth of *P acnes* [3]. And Staphylococci were the first

organism that colonized the normal skin people [4].

Staphylococcus epidermidis were found as comensal (normal colony at nares, head and axilla) and patogen (as chronic nosocomial infection that infected through contaminated stuff in cardiac cathetherization or other procedures). It was difficult to be eradicated, it had high resistances, it was easy to be infected again after it was treated (by hands or contaminated stuff) and it was clinically found as chronic infection. But this colonization inhibited *Staphylococcus aureus* virulencies [7].

Pityrosporum ovale was lipophilic, saprophytic, budding, unipolar, dimorphic gram positive, double walled, oval to round yeast. They were normal part of the follicular skin flora, and alteration in flora caused uncontroled growth of yeasts and would been pathogenic [4]. They needed free fatty acid for survival (they had lipase that hydrolized triglyceride to free fatty acid). They were found in stratum corneum and in pilar follicles in areas with increasing sebaceous gland activity such as chest and back [8].

P acnes were gram positive, non motile, rods that tended to be irregular when the first isolated - some were short branching and required free fatty acid to colonize [3,4]. *P acnes* should been clumped, free fatty acid aided clumping, and so bacterial lipases might been necessary for clumping and for ductal colonization [3]. Isolates required 7 days of incubation under an aerob conditiom in 35-37°C (but this organism was not strickly an aerob) [4]. The physiological microenvironment of the follicle and the microenvironmental adaptation of *P acnes* might been important factor in the penetration of this non motile bacterium into the follicle duct [4]. They grew optimum at 30-37oC (temperature in the follicle) [4].

The environment of the bacteria was probably more important than their absolute number for development of acne lession [3]. In vitro, it had been shown that low oxygen tension, acidic pH and nutrient supply [nitrogen, carbon, hydrogen, carbohydrate, amino acid, minerals, vitamin (biotin, nicotinic acid and thiamin) markedly affected the growth of *P acnes* and the bacterial of active substances production such as lipase, proteases,hyaluronate lyase, phosphatase and smooth muscle contracting substance [3,4,6,7].

In the presence of light at high oxygen concentrations, *P acnes* grew well, but later the growth was inhibited because of photodamaging reactions involving excess oxygen and the endogenous microbial porphyrins [3]. The development of acne vulgaris was likely linked with the *P acnes* and very occasionally with the transient flora that were involved in acne (The transient flora was gram negative bacteria that was shed from anterior nares onto the adjacent skin after the resident flora was supressed by long term systemic or topical antibiotics) [3,4]. The limitted species of organism (resident organism) colonized the skin surface, such as propionibacteria, staphylococci, aerobic coryneform bacteria and the yeast *Malassezia furfur* [4]. Some microorganisms were appeared and dissapeared from the skin environment and constitued transient flora [4].

4. Inflamation processes

Cunlife reported that hystologically CD4+ T lymphocytes were found in eatly 6 hours papular acne inflammation, CD4+ T lymphocytes and neutrophyl were found in 24-48 hours, CD4+ T lymphocytes, macrophage and giant cells were found in 72 hours [4].

The dermal inflammation was not been caused by bacteria in the dermis. It was probably resulted from biologically active mediators (IL 1α, IL β, TNFα,etc) that diffused from the follicle where they were produced by the binding of bacterials to TLR2 receptor (or others) of monocytes, sebocytes, keratinocytes, perifollicular and peribulbar macrophages, langerhans cells and other immune cells or CD4+ of T lymphocytes [4,6,10,11]. There was an ability of innate immune system to use TLR2 receptor to recognonized microbial pattern and initiated immune response in cutaneous disease [9]. TLR 2 receptor induced inflammatory response and the development of antigen spesific adaptive immunity [6].

Pro inflammatory cytokine stimulated abnormal keratinocyte proliferation,differentiation and hypercornification that revealed obstructions, than there were follicles impaction and distention that formed comedos [2,3,9]. As the retained cells blocked the follicular opening, the lower portion of the follicle was dilated by entrapped sebum. Disruption of the follicular epithelium permitted the discharged of the follicular dermis [2]. The combination of keratin, sebum and microorganism led to pro inflammatory mediators releasing and lymphocytes, neutrophyls and foreign body giant cells accumulating [2]. In the early inflammation, inflammation was due to pro inflammatory mediators that moved through the duct wall into the dermis, and had not been caused by the duct ruptured [3]. Interleukine1α was a dominant proinflamatory cytokine that played role in comedonal acne vulgaris inflammation process [4]. Other pro inflamatory cytokines that were produced were IL6, IL8, IL12, IL4, IL10, TNFα [4].

Some kind of pro inflammatory cytokines that were produced by innate immunity in acne vulgaris in some journals were :

- ✓ TLR 2 receptor of the monocytes bound to *P acnes* to produce IL12, IL8 pro inflammatory cytokine [10].
- ✓ NLRP3 inflammasome of the human sebocytes and monocytes as mediated pathway bound to live *P acnes* in the sebaceous glands through caspase 1 expression & activation to produce IL1β [11,12].
- ✓ TLR 2 receptor of the keratinocytes bound to *P acnes* to produce IL8, human defensin 2 pro inflammatory cytokine [10].
- ✓ TLR2 receptor of human keratinocytes bound to *P acnes* through PAMPs-Pathogen Associated Mollecular Paterns to produce IL1α in 7 days of exposures that induced comedogenesis [13]. PAMPs were such as peptidiglycan (PG) and lipopolysacharida (LP) of *P acnes* [6]
- ✓ PAR 2 of the keratinocytes bound to *P acnes* to produce IL 1α, IL8, TNFα [10].
- ✓ TLR2 receptor of human monocytes and skin surface macrophages in human pilosebceous bound to microbial agent (*P acnes*, gram positive coccus) through NFkB/Nuclear Factor kappa light chain enhancer of activated B cells activation and MAPK (Mitogen Activated protein Kinase) cascade to sinthesize and release of IL12, IL8. TNFα, IL1β [6,14].
- ✓ TLR 2 receptor of monocytes bound to gram positive coccus to produce IL12 [14].
- ✓ Monocytes bound to *P ovale* (lived or heat killed, opsonized *P ovale* through alternative complement activation pathway more stimulated than non opsonized) to produce IL8, IL1α [15].
- ✓ Monocytes bound to gram positive bacteria to produce TNFα, IL6 [15].
- ✓ Monocytes bound to Gram negative bacteria bound to produce TNFα. IL1. IL6 [15].

IL 8 induced chemotactic factors might played an important role in attracted neutrophyl to the pilosebaceous unit that led to release lysosomal enzime that led to rupture follicular epithelium and further inflammation [14]. Furthermore *P acnes* released lipases, proteases, hyaluronidase which contributed to tissue injury [14]. IL 8 induced chemotaxis and activation of neutrophyl and T cells [15]. IL12 promoted development of Th1 mediated immune response. And overproduction of Th1 cytokine such as IL 12 was implicated in the development of tissue injury in a certain autoimmune and inflammatory disease [14].

IL1α was low activated by lymphocytes, chemotaxis, activation of neutrophyl than induced inflammation [15]. Therefore interaction of *P ovale* and phagocytic cells might served to amplify the inflammatory response and encourage further recruitment of phagocytic cells [15]. P ovale upregulated phagocytic cells (macrophages) thus provided enhancer protection to bacterial and tumor cells [15]. There were down regulated of pro inflammatory cytokine with removed lipid [15]. Langerhans/macrophages were able to take up antigen (acted as antigen presenting cells/APC) and then were presented to T cells [15].

P acnes activated monocytes cytokine relased through the pattern recognition receptors (PPRs), for example TLR2 receptor of the innate immune system [14]. So TLR 2 receptor was PPRs [14]. TLR2 receptor activation contributed to the pathogenesis of acne, suggesting that these cells promoted inflammatory responses at the site of the disease activity and induced pro inflammatory cytokine production [14]. Release of pro inflammatory cytokines that were mediated through TLR2 receptor had harmful effect in acne by promoting inflammation and tisuue destruction [14]. So TLR 2 receptor was a logical target for therapeutic intervention to block inflammatory cytokine response in acne and other inflammation condition which tissue injury was detrimental to the host [14]. Isotretinoin down regulated TLR2 that induced cytokine response [6].

Infestation of the organism itself was not the main caused of the disease but was rather caused by the various inflammatory responses that were initiated by microbial agents that led to destruction of the host tissue. Such responses were : the formation of immune complex, the recruitment and activation of neutrophyl and monocytes, the released of cytokines, released of dependent enzymes [14].

P ovale had 2 phenotypes, immunostimulated and immunosupressed phenotypes, P ovale (through an alternative pathway of complement activation) activated cellular immune response and humoral immune response [15]. Complement was the part of immune system that enhanced the ability of antibodies and phagocytic cells to clear microbes and damage cells from an organism, promoted inflammation and attacked the pathogen plasma membrane. It was part of innate immune system (which was not adaptable and did not change over the course of individual`s lifetime) and it could been recruitted by the adaptive immune system to finish the action.. There were 2 complement activation : classical pathway (that was mediated by immune complex) and altenative pathway (that was mediated by yeast or bacterial cells) [15]. There was complement activation that involed in the early to later stages of inflammation and *P acnes* were capable for triggering both the alternative and classical complement pathways [1,3,4,15]. Complement activation caused lysis bacteria and virus, opsonization, inflammation [15].

In the early non inflamed and inflammed lession had shown that there were activation of the classical and alternative pathways [3]. And there were the type 4 immunological reaction to a non spesific antigens in the prior of obvious duct ruptured [3].

The majority comedones clearly represented a dermal pool of pro inflammatory IL 1α [4]. Spongiosis of the pilosebaceous follicle wall was the feature of early inflammation changed, this could led to leakage of comedonal IL 1α into the epidermis [4]. The consequence was the activation of dermal microvascular endhothelial cells, selective accumulation of antigen non spesific to mononuclear cells and inititation of antigen independent cutaneous inflammation that consistent with the hystological features of early inflammation in acne [4].

In the later, in the moderate and severe inflammation , there was disruption of the duct and macrophage giant cell foreign body reaction [3]. An amplification phase via antigen dependent T cell responses to other comedonal components for example *P acnes*, might then developed [4]. The intensity and duration of the subsequent cell mediated response would been depended on many factors, including the degree of individual sensitization to their cutaneous microflora [4]. Following the disruption of cell wall, neutrophyl would been attracted into the duct by microbial chemotactic factor, that was proved by a study that demonstrated the capability of *P acnes* to attract neutrophyl in vitro [4]. So *P acnes* might caused inflammation because this organism had been shown to secrete chemotactic factors and the chemotactic activity had been shown in comedones [1]. Low mollecular weight chemotactic factor did not require serum complement for activation and because of its small size, it could probably escaped from follicle and attracted polymorphonuclear leukocytes [1]. If polymorphonuclear leukocytes enter the follicle, they could ingested *P acnes* organisms, resulted the release of hydrolytic anzymes which in turn, might been importance in producing follicular epithelial damage [1]. Polymorphonuclear leukocyte ingested *P acnes* was anti *P acnes* dependent antibody (ADCC) [1].

Bacterial cell walls fractions of *P acnes* were a potent chemoattractan for polymorphonuclear and mononuclear cells, could also produced prostaglandine like substance, that acted as non streroidal anti inflammatory drugs, that had small anti acne effect [3].

It was likely but was not been proven that *P acnes* played an important role in acne inflamation [4]. Whether *P acnes* played a role in the initiation of inflammation in acne was questionable since it had not been colonized at all of the early lessions. Nevertheless, there was an increasing in the number of lessions colonized by *P acnes* following early inflammatory change. *P acnes* were a potent adjuvant that induced a chronic inflammatory tissue response because it was resistant to phagocyte killing and degradation [4]. So *P acnes* caused chronic inflammation process because of its resistance to phagocyte cell and could not been degraded [4].

In the late phase of inflammation, *P acnes* dependent T cell lymphocyte response could been found, there were variations in Cell Mediated Immune Response depended on individual microflora sensitization [1,4]. Circulating antibody to *P acnes* were elevated in patient with severe acne [1]. Patients with severe acne were significantly more sensitized to *P acnes* than normal individuals, and the overall immunological status of patients were elevated

compared with acne free individuals of the same age [4]. But this observation did not provide direct evidence for a pathogenic role of *P acnes* in initiating inflammatory acne and might merely reflected an increased exposure of patient to the organism as result of their condition and might played a role in the exacerbation of chronic inflammatory response [4].

Lipid that got into dermis when the duct ruptured acted as an irritant and some lipids like linoleic acid could down regulated neutrophyl oxygen metabolism and phagocytosis, and contributed inflammation [3]. Inflammation was resulted from the production of free fatty acid and it showed that *P acnes* was the main source of follicular lipase that hydrolized trigliserida to free fatty acid [1]. The sebolemmal sheath accumulated inspisated sebum and formed a firm calculus which eroded the duct wall and contributed to inflammation [3].

DHT was the main driver of androgen induced sebum production of the skin. DHEA was another hormone for increasing sebaceous gland activity. Increasing DHEA secreted in adrenarche (puberty) could increased sebum synthesis. Sebum rich environment made skin *P acnes* grew and caused inflammation around follicle due to activation of innate immune system that increased pro inflammatory cytokines IL1α, IL8, TNFα, LTB4 production, than cytokines attracted various immune cells to the hair follicles (neutrophyls, macrophages, Th1 cells). IL 1α stimulated and triggered keratinocytes activity and reproduction which turned fueled comedo development [16].
P acnes provoked inflammation by altering sebum fatty composition [16].

1. *P acnes* oxydated squalene that
✓ Activated NFkB and consequently increased IL 1α levels.
✓ Increased 5 lipooxygenase enzym that responsible in arachidonic acid pathway- leukotriene B4 (LTB4) that promoted skin inflammation by acting on peroxisome proliferator activated receptorα (PPARα). PPARα increased activity of activator protein (AP1) and NFkB led to recruitment of inflammatory cells. AP 1 inflammatory cascade led activation of matrix metalloproteinase which contributed to local tissue destruction and scar formation [13].

2. *P acnes* Hydrolized triglycerides to pro inflammatory free fatty acid through lypase enzyme of *P acnes*. FFA spur production of antimicrobial peptides/AMPs (Such as Human β defensin 1/ HBD1, cathelicidine, human β defensin 2/HBD2) thus leading to further inflammation.

That inflammation in acne lession was broken in the deep layer and formed nodules, In study was reported the elevated IgE levels that related with clinical severity in a group, but another group was found no changed in total IgE levels [3,16]. Female had better defence mechanism than male against *P acnes* [3]. Most acne patient had no misfit immunological reaction [3]. There were no circulating immune complexes in acne sera patients [3]. Skin testing with heat killed suspensies of *P acnes* demonstrated that subject with severe acne produced a greater inflammatory reaction at 48 h than other subject, suggested that host response might been important [3]. Changing in neutrophyl chemotaxis might been the secondary event [3]. *P acnes* polypeptide were detected in serum of the acne patients but were not in normal individu.3 Acne fulminant showed exaggerated delayed hypersensitivity reaction to *P acnes* [3].

Affected & predisposed factor

Several factors that affected, predisposed, triggered, influenced, exacerbated or aggravated acne vulgaris were: genetic, racial, atopic, seborhoeic, mestruation, hormonal misfit, diet, environment. ultraviolet light, hot and humidity, sweating, friction, occupation, stress, cosmetic, pomade [4].

Genetic. There were multifactorial genetical background and familial predisposition that had been proved in twin study [1,3]. Acne was polymorphous dermatosis with a polygenetic background, that did not follow Mendelian rules [4]. Most individual with cystic acne had parents with a hystory of severe acne [1]. Several study had shown that genetic factor influenced susceptibility to acne [3]. There were 45% acne parents`s in schoolboys acne patient in Germany and were also supported by genetic study in twins [3,4]. Besides genetic factor, the exogenous factor also influenced the severity of disease inflammation process, for example bacterial colonization [4]. Severe acne might been associated with XYY syndrome (rare) [1].

Racial. Acne in Black Americans were less evident than white Americans. Americans had more severe acne than Japanese [3]. Acne vulgaris was lower incidence in Asians and Africans [1].

Atopic. There was decreased incidence of acne vulgaris in atopic dermatitis patients that had low sebum production [3].

Seborrhoeic. Seborrhoeic dermatitis was concomitantly found with acne vulgaris in some cases, but the relationship had not been known [1].

Menstruation. About 70% patient reported 2-7 days premenstrual flared up of acne vulgaris related to sebaceous pores size changing that influenced the hydration of pilocebaceous epithelium [3,4]. There was an alteration of progesterone and estrogen levels [3,4]. Estrogen therapy increased SHBG and reduced free testosterone so there were decreasing of sebum production and libido [17].

The orifice of pilosebaceous duct was smallest between days 16-20 of the menstrual cycle. It reduced the flowed of sebum, produced relative obstruction and so increased the possibility of pro inflammatory cytokine mediators to concentrate in the lumen of sebaceous glands duct, thus stimulated the flare of acne premenstrually [4]. There was premenstrual changing in hydration of pilosebaceous epithelium and variation in sebum excretion during pre menstrual cycle that flared acne[3]. Testosterone was produced by ovarium and adrenal gonad, testosterone than converted to estrogen and progesterone [17]. Testosterone levels peaked at the middle of menses phase (was around of ovulation) and there was increased libido [17]. Testosterone was converted to DHT by 5α reductase enzyme. Testosterone and DHT were androgen that stimulated and were binded to androgen receptor in the sebaceous gland thus stimulated sebum production [17]. Most of acne female had normal menstrual cycle and normal hormonal level [4].

Hormonal misfit. In 24% acne vulgaris patient had no hormonal abnormality. Most acne patients had normal hormone levels or levels at the upper end of normal range [3]. Most acne patients had no hormonal misfit, and had no need to investigate the hormonal problems in female patient [4].

Active sebaceous glands were required for the development of acne

vulgaris [3]. Sebaceous activity was predominantly depended on androgen of gonadal and adrenal origin [3]. In the normal level of androgen production, there were increasing stimulation of sebum production in sebaceous gland of acne vulgaris patient There was also a possibility of an end organ hyper response of the pilosebaceous glands to normal circulating levels of androgen hormones [1,4]. And it was supported by the finding that the sebaceous glands in acne prone areas function differently to those in non prone areas, so acne could been found only on the trunk and none on the face, or acne just on the face and none on the back and chest [4].

Acne vulgaris patient extended on average more sebum than normal subject, the level of secretion was correlated with the severity of acne [3]. Androgen hormone had pro inflammatory effect, so androgen levels and antiandrogen therapy influenced acne inflammation severity [4].

There were rare cases with excessive androgen production of ovarium, adrenal and pituitary that were found in some exceptional case like acne in children (5-7 years), individual who poorly responded to 3 course oral isotretinoin acne therapy, patient with clinical skin androgenic manifestations like excessive hair, hoarse voice, irreguler menstruation, could not got on well with the men, could not been pregnant and female pattern alopecia (in polycystic ovarian syndrome and congenital adrenal hyperplasia) [4].

Diets. Cunliffe said that overall dietary factor did not cause acne [4]. In study proved no correlation between acne severity and whatever food ingestion [4]. In personal study there were no link between acne severity, calory intake, carbohydrate, lipids, protein, minerals, amino acid and vitamin [4].

But the possible effect of nutrition on the age of puberty might been relevant, as acne was more likely occured after the started of sexual development and this occured when the body weight attained about 48 kg [3]. The insidens of acne was low in people who had eaten rich fish diets and that was markly increased acne insidens in people who had eaten western diet with saturated fat [3]. It could been due to genetic factor.4 Environmental factor also influenced the kind of people diet [3].

Chocholates, caramels and fatty acids were accused of aggravating acne [4]. High glycemic diets aggravated acne [2]. Chocholate had insuline like substance [2]. In high insulin levels, there were low SHBG levels and high free testosterone levels that increased sebum production. Insulin might affected SHBG, thereby influencing androgen clearance [3]. There was an inverse relationship between the serum levels of insulin and SHBG in woman [17]. In obesity there was raised insulin levels, lower SHBG levels & total testosterone in both sexes [14]. Lower SHBG resulted in increasing of free testosterone, the effect of high free testosterone levels resulted masculinization and high sebum production. Estrogen therapy increased SHBG and reduced free testosterone so there were decreasing of sebum production and libido [17].

However post meal transient hyperinsulinemia did not play a role in hyperandrogenaemic acne patients [3]. And in study, high chocholate diet did not modulate the natural course of acne [4]. Chocholate appeared to have no significant influence in acne course study [3].

Reduced skimmed milk diet with calsium and vitamin D suplementation were benefit in acne patient and obesity [2]. Continuous low calori intake such as in anorexia nervosa patient and in patient with crash diet might improved the disease, and there were reducing of sebum excretion rate, changing sebum composition, decreasing sex hormones such as DHEA that explained clinical improvement of acne [4]. Dietary restriction resulted a mark weight loss and reduced seborhoea, but it could not been considered as routine treatment for acne.3 Crash diets that were combined with strong physical stress could increased androgen release [4].

Environment: Acne insidence increased in people who migrated from east to western countries because of the dietary changing (rich fish diet to saturated fat diet), due to environment factor that influenced the people diet [4].

UV radiation: UV radiation was known to have wide ranging effect on cellular immunological system, but controled study on the therapetic effects were lacking [4]. UVA could converted squalene into squalene peroxidase which could enhanced comedogenesis4 But the other UV radiation like UVB, visible light (blue and red) and natural light 400-450 wavelength were beneficial to improve acne lession [4]. Artificial UV radiation appeared to be less satisfactory than natural radiation [3]. UVB produced tanning of the skin that produced camouflage that led to a subjective improvement of acne [4]. Erythemathous and suberythemathous dose of UVB could led to scalling of the interfollicular epidermis and might helped corneocyte desquamated from around of acroinfundibulum [4]. Narrow band UVB particularly helped in eczema and psoriasis [4]. The wavelength 400-450 nm could activate porphyrins (in the bacteria) that were produced by *P acnes* and could helped to destroy *P acnes* in the acne follicles themselves [4]. Visible light in both red and blue light range had been shown to improve acne as effective as benzoil peroxide. It was suggested that red light was antimicrobial [4]. Photodynamic therapy was under invenstigation [4].

Sweating: Up to 15% patient noticed that sweating caused a deterioration in their acne, especially if they lived or worked in a hot humid environment, for example as a cook. Ductal hydration might been a responsible factor [3].

Hot and Humidity: Acne could been worsen dramatically if patients were exposed to tropical and subtropical climates [4]. The holiday to humid environment frequently precipitated acne [4]. It might related to increase poral occlusive effect of skin hydration [4]. Excess humidity aggravated acne by an effect on sebum outflow [4].

Friction: Friction might contributed additional acne by irritating the upper parts of pilosebaceous duct [4].

Occupation: Hydration of the ductal stratum corneum induced acne in such occupation like catering. Acneiform oil folliculitis and chloracne were the occupational acne [4].

Stress: It was unlikely that stress alone induced the formation of acne lession. However acne itself induced stress and picking of the spot would aggravated the appearance. That was particularly obvious in young females who presented acne excoriee. Questionaire study had shown that many patients experience shame(70%), embarrassment and anxiety (63%), lack of confidence (67%), impaired social contact (57%) and significant problem with unemployment Severe acne might been related to increase anger and anxiety. There

were psychological and social effect of acne in inducing anxiety, depression and impaired the quality of life [4].

Cosmetic: It had shown that some cosmetic contained lanolin, petrolatum, certain vegetables oil, butylstearate, lauryl alkohol, oleic acid, isopropyl myristate, propylene glycol, D and C red dyes were comedogenic[3].

Pomade: Pomades were comedogenic greasy preparation [3].

Course & Prognosis

Acne vulgaris frequently cleared spontaneously by the early twentieth but could persisted to the fourth decade or older [1]. Treatment for acne might only required for 3-4 years, but the many patients with obvious clinical acne therapy would required for 8-12 years until the acne went into spontaneous remision. Spontaneous remission frequently was around the age of 25 years, 93% of acne cases were resolved within 25 years and in 7% acne could persisted well into the mid forties or early fifties (up to the age of 45 years) and they were called as mature acne [4].

Inflammed lessions developed dynamically, with the majority exhibiting polymorphic clinical and hystological appearance before resolving. Papule might become pustular before resolving, ussually through the macular phase. Over 50% of superficial lessions were resolved within 7-10 days, whereas the deep seated nodules and pustules might persisted for 10-30 days or even longer [4]. The lessions would been healed and exacerbated by many factors and made acne vulgaris as one of the chronic pilosebacebaceous disease [1,3].

Flares occured in winter and with the onset of menses.1 Several factors that affected, predisposed, triggered, influenced, exacerbated or aggravated acne vulgaris were genetic, racial, atopic, seborhoeic, mestruation, hormonal misfit, diet, environment. ultraviolet light, heat and humidity, sweating, friction, occupation, stress, cosmetic, pomade [4].

The squele of acne was scarring that might been avoided by early treatment, espescially with oral isotretinoin early in the course of the disease [1]. Early recognition and treatment of acne were important to prevent physical scarring espescially in inflammatory acne that could caused many psychological distress [4].

Limitted studies suggested that resolution did not relate to reduction of sebum production or surface bacteria. Pierard had shown that there was an individual sebaceous glands function at different rates in acne patients. The resolution associated with spesific changed in these acne prone hypersecreting glands [3]. The relationship between ductal hypercornification, inflammatory mediators, changed in the host response and resolution was obscured [3].

Complication

Acne scars were acne vulgaris complication event with the excellent treatment available were performed [2]. Intense inflammation led scar formation [1]. Scars were frequentlly occured in cystic acne, but less severe lessions also formed scar [2]. There were 2 sorts of scarring [3,4]:

1. There was loss of scar tissue (ice pick scar, depressed scar, macular atrophic scar, perifollicular elastolysis)
2. There was an increased of collagen tissue (hypertrophic scar, keloid scar)

Pitted scars/ice pick scars were typically occured on the cheeks. Perifollicular elastolysis was predominantly occured on the back, chest, neck. Keloid could been seen along the jawline and chest [2,4]. Scar might improved spontaneously over 1 year or longer [3]. The rare scars complications were calsifications [3].

Other complications from acne were [3]:

- ✓ Prominent residual hyperpigmentation which was especially happened in darker skinned patients
- ✓ Pyogenic granuloma formation which was more common in acne fulminans and in patients treated with high doses isotretinoin
- ✓ Osteoma cutis which was consisted of small-firm-papules resulting from long standing acne vulgaris
- ✓ Solid facial oedeme, which was a persistent form facial swelling that was an uncommon but distressing result of acne vulgaris or acne rosasea.

Antibiotics resistances were the commonest complication. It was due to prolong treatment of acne vulgaris that was needed because of the disease chronicity [3,4]. Given treatment combination, changed the dose and duration of antibiotic therapy, given oral isotretinoin and the other non antibiotics regimen could solved the resistances to antibiotic problems [3]. The rare long term treatment of acne with antibiotics complication was gram negative folliculitis [3]. The lession appeared on anterior nares and extended to adjancent skin [1]. The physician should changed the diagnosed if there were suddenly appeared pustules and nodules [1].

There 2 kinds of gram negative folliculitis lessions were [2]:

1. Multipel pustules that were based on wide inflammation areas. It was more frequent. The etiology was Enterobacter and Klebsilla.
2. Deep indolent nodules. The etiology was Proteus.
3. Bacterial cultures and sensitivity tests should been performed to decide the prompt treatment. Ampicillin and trimetoprim were the treatment of choice for gram negative folliculitis. Oral isotretinoin was choosen for the resistent antibiotics cases [2,3].

Acne Variant/Acne Subtypes

The acne vulgaris variants were severe acne variant (acne conglobata, acne fulminans, pyoderma fasciale/rosacea fulminans), neonatal acne, infantile and juvenile acne, acne excoriee and dysmorphophobia, drug induced acne/acneiform eruption, endocrine acne, externally induced acne (cosmetic acne, pomade acne, occupational acne due to oils and tars, chlor acne, mechanical acne, detergent acne, tropical acne/hydration acne), pilosebaceous naevoid disorders, naevus comedonicus, familial comedones, solar comedones/actinic.senile comedones, hydradenitis suppurativa like acne/acne inversa, SAPHO syndrome.syndrome associated with acne, PAPA syndrome [1,3,4].

Differential Dignosis

The differentials diagnosis of acne vulgaris were acneiform dermatosis, acne steroid, drug induced acne, acne aestivalis, acne agminata, acne varioliformis, adenoma sebaceum, boils, dental sinus, human immunodeficiency virus, folliculitis (Staphylococcus aureus folliculitis, Staphylococcus epidermidis folliculitis, demodex folliculitis, fungal folliculitis, Pityrosporum folliculitis), milia molluscum contagiosum, perioral dermatitis, plane warts, rosacea, seborrhoeic dermatitis, sycosis barbae, syringoma, trichoepitheliomata [1,4].

The differential diagnosis of acne scars were hidroavacciniforme, ulerythema ophryogenes, atrophia maculosa varioliformis cutis, porphiria cutanea tarda [4].

Treatment

Goal of therapy: The goal of therapy were: removed plugging of the pilar drainage, reduced sebum production, treated bacterial colonization and prevented from scarring [1,4]. The treatment might been required for 3-4 years, patient with obvious clinical acne required 8-12 years therapy until the spontaneous remission was occured. Spontaneous remission wouldl been occured in 25 years old and 7% could persisted until mid forties-early fifties and were called as mature acne [3,4].. Early recognition and treatment of acne was important to prevent acne scarring that caused physiological distress [4].

Treatment modality:

The treatment modality were :

1. Topical therapy : topical antibiotics (Erytromycin, clindamycin), benzoil peroxide, sulphur, resorcinol, salisilic acid, retinoic,azeleic acid
2. Oral therapy : oral antibiotics (doxycycline, tetracyclne, minocycline, amoxycillin, erytromycin, clindamycin, sulfa, dapsone) , oral isotretinoin [1-4].
3. Physical therapy : intralessional triamcinolone acetonide, cryotherapy, comedo extraction, cauterry, chemical peeling, photodynamic terapy, excision, surgical for severe and resistant cases [1-3].
4. Hormonal therapy had good result in normal or abnormal laboratory test patient. Spironolactone and cyproterone acetate treated acne vulgaris by reducing sebum production, reducing androgen excess and alleviating cystic acne [3,4]. Other hormonal therapy reduced sebum production by reducing testosteron level, but clinically had serious side effect (finasteride, flutamide, estrogen, gonadotropine releasing agonist and metformin). TNF inhibitor (etanercept etc) [2].

Treatment of complication

The complications were acne scar, persistent hyperpigmentation, pyogenic granuloma formation, persistent form facial swelling and could been treated by laser, chemical peeling, skin needling and rolling, dermabrasion, laser dermablation, cryopeeling, filler, punch graft, intralessional steroid and fluorouracyl [3]. The rare long term treatment of acne with antibiotics complication was gram negative folliculitis [3]. Ampicillin and trimetoprim were the treatment of choice. Oral isotretinoin was choosen for the antibiotic resistance cases [2,3].

Chemical Peeling

Chemical peeling was one of the treatment of choice for acne and acne scar [17,18]. Chemical peeling/chemical resurfacing/ chemoexfoliation/chemosurgery involved an application of one or more exfoliating agents to the skin, resulting in the destruction of portion of the epidermis and/or dermis with subsequent regeneration. This produced controling wound and reepithelialization [19].

Acne vulgaris might been improved by superficial peeling, although medium peeling could aggravated or actually produced acne [19]. In rosasea the existing erythema of the disease made medium peeling more risky because of persistent tenderness or erythema [19]. Chemical peeling generally treated superficial acne scar [4]. Medium depth peeling with solid CO2 to efface the rims or the edge of depressed scar, was combined with immediate repetitive application of 35-50% TCA to the rims, had resulted in substantial improvement [19].

Chemical peeling could been used to improve the appearance of ageing, wrinkled or sun damaged skin [17]. It was less effective in dealing with acne scars but it was a valid dermatological manouvre for these and the other superficial lessions on the face [17]. Chemical face peeling was given to conjunction with or as an alternative to dermabrasion. There were many protocols involved in different combination of chemical peeling, some were given in combination with laser dermablation [4].

A variety of preparation on differing concentration could been given alone or in combination, depending on the desired outcome.17 Peels were categorized by the level of injury they caused [17].
Chemical peeling wounding classification, divided into 3 types [18,19]:

1. Superficial peeling wounding-to stratum granulosum/papillary dermis
   a. Very light-stratum corneum exfoliation or stratum ghranulosum depth (α hydroxy acid, salisilic acid, TCA 10-25%, resorsinol, jessner`s solution, solid carbondioxide, tretinoin),
   b. Light-basal layer or upper papillary dermal depth (35% TCA unoccluded, single or multiple application)
2. Medium depth peeling wounding-through the papillary dermis to upper reticular dermis
   a. Combination peels, single or multiple applications (CO_2+TCA35%, Jessner`s solutions+TCA 35%, Glycolic acid +TCA35%, 50% TCA unoccluded single applications)
   b. Full strengthth (phenol 99% unoccluded).
3. Deep depth peeling wounding to the mid reticular dermis (Baker Gordon, baker phenol croton oil unoccluded and occluded).

Patients with dry skin and fair complexion were the best subjects [17]. Fitzpatrick`s classification measured pigmentary responsiveness of the skin to ultraviolet light most often based on ethnic background. Skin type I-III were ideal for peeling, types IV-VI could also been peeled with all peeling agent but the risk of unwanted pigmentation was greater [19]. The neck should only been included with caution as the skin in this area was more prone to scars and hyperpigmentations [17]. Weaker preparation were generally applied on eyelids and the care should not been taken to cause hypertrophic scars, which might occured around the mouth or mandible [17]. Prolonged erythema and increased sensitivity to sunlight and pigmentary changed (both hyperpigmentation and hypopigmentation) might followed the procedure [17].

In acne vulgaris, chemical peeling had keratolytic effect by dissolved intercellular cement and reduced corneocyte adhesion, anti inflammatory effect by commedolytic action (Salisilic Acid was better) and bactericidal action (Glycolic acid was better) [20].

Peeling in acne: Chemical peeling was given as an adjunct to medical therapy in acne, because it produced complimentary rapid therapeutic effect and improvement in skin appearance and texture [21]. Primary effect was in comedone with a concomitant reduction in inflammatory lessions. Peels allowed topical agent to penetrate more efficiently into the skin and might improved PIH [21]. Peeling agent for acne : SA, GA, LHA, Jessner`s, TCA [17,21].

Peeling for post acne hyperpigmentation and rejuvenation: Chemical peels were evidence based in treatment of post acne pigmented macules and atrophic scars as they improved coexisting comedonal and papular acne, reduced post acne erythema and have a lightening effect on pigmentation at the base of healed lessions and scars [22]. Chemical peeling improved the depth contour and caused softening associated scars by their action on collagen remodelling and stimulation of new collagen activity [22]. All peels also added improvement in texture glow [22]. Chemical peeling also acted as priming for treatment of pigmented acne marks in skin of colors before resurfacing therapies with lasers and lights were sought for [22]. Chemical peeling was thinning the stratum corneum and regenerating a compact epidermis which reflected light evenly acrossed the skin surface and imparted a textural improvement and lightening effect by the elimination of epidermal melanin and prevention of transfer of melanin to keratinocytes [22]. Chemical peeling was resultant improvement in dyschromias, texture and fine lines. And rejuvenation effect was enhanced if the patients was well primed espescially in dark skin types [22].

Priming: Daily application of 0,1% tretinoin for 2 weeks prior to 35% TCA peels significantly enhanced the healing time of the facial, forearm and hand skin in a double blind placebo controlled study [19]. However tretinoin application before and after TCA did not significantly enhance the clinical efficacy of the peel [19]. Topical tretinoin all trans retinoic acid was a suplement to most peel regimens along daily application of sunscreen [19].

Contraindication of chemical peeling: Those patient who were not closely cooperating with physician should not been treated [4]. There was evidence that patients should been off oral isotretioin for 1 year. Frequently relapsing herpes simplex was a relative contraindication [4]. Occasionally herpes simplex infection was an absolut contraindication and acyclovir prophylactic could been prescribed [4]. Peeling should not normally been performed during the sunny time of the year, because of the greater possibility to produce hyperpigmentation post therapy[4,17].

Complication of chemical peeling: Pigmentary changed in the form of hyperpigmentatiom might occured in darker skin types and was caused by sunlight, estrogens, photosensitizing drugs or pregnancy. Baker gordon depth peels could made hypopimentation and scarring. TCA 50% was capable of unpredictable hypertrophic scarring and hypopigmentation. Bacterial, fungal, viral infection might occur after peeling. Prolong erythema might occur after peeling and might been treated with topical hydrocortisone. Redness occured in patient who took alcohol beverages, suffered from contact dermatitis and took isotretinoin prior peel. Textural skin changed and the form of large pore occured temporarily after peeling. Skin atrophy, cardiac arythmia, laryngeal oedeme, exacerbation of koebnerizing pemphigus like disease might occured in phenol/croton oil peels [19].

Peeling Agent

TCA

TCA was probably the most commonly applied agent [17]. Weak preparation 10-15% might been applied for light freshening peels and higher concentrations for medium depth or deep peels [17]. The depth of injury was depended on acid concentration and the number of application. Need no neutralization [17]. TCA 10% was superficial chemical peeling, considered as adjunctive therapy in acne, often added to the first line therapy such as retinoids and antibiotic, and as the first line therapy for acne scar and skin rejuvenation [19]. In high concentration was good for treating acne scar (CROSS/ Chemical Reconstruction of Skin Scars technique) [4,19]. TCA was cheap and save because no systemic absorbtion, but it felt pain (more than SA,less severe than phenol) [19].

TCA was an effective haemostatic caustic, which had many uses [17]. The 30-50% concentration could been given as styptic and was frequently employed as conjunction with superficial curretage in the treatment of solar keratosis, seborrhoeic warts, etc [17]. The supersaturated solution could been applied on its own to treat many benign and dysplastic skin lession [17].

TCA was useful treatment for xanthelasmata and solar lentigos [17]. It should been applied with great care, however, especially around the eyes [17]. Its action was rapid and white frosting occured within a few seconds of application. The caustic action could been partially neutralized by applying alcohol, water or sodium bicarbonat soaked gauze but this was unlikely to have any effect once the acid had penetrated the skin [17].

Excess sebum should first been removed using detergent, ether or acetone [17]. TCA should then been applied with an almost dry applicator. The concentration that was applied could vary according to the site, the condition to be treated and whether the TCA was being applied as a styptic or a superficial skin caustic [3]. Weaker solution of TCA were sometimes given for treating wider areas of skin [17]. Because of deliquisence TCA should been kept in close, coloured and corrosion resistant bottle [17].

TCA 50% was similar to phenol in its destructive effect on the epidermis [17]. TCA chemical peeling caused epidermal coagulation and collagen necrosis up to the upper reticular dermis, reepithelialization begun from survival islets of keratinocytes and skin appendages and the clinical effects were due to resultant increased in dermal volume of collagen, glycosaminoglycans and elastin [17,19]. Keratolitic and comedolitic effect of TCA diminished free fatty acid that was important for bacteria and fungal growth, so it acted as antibiotic and antifungal adjuvant therapy and could solved resistance problems to antibiotic and antifungal in acne therapy.

α hydroxy acid (AHA, Lactic acid, glycolic acid, malic acid).

α hydroxy acid was mild [17]. α hydroxy acid for example glycolic acid could acted as superficial peels or freshening peels and at high concentration as medium depth chemical peels [17]. The depth of injury depend on pH, concentration of the acid, amount applied/layer and duration/length of treatment time [17]. Should been neutralized [17].

AHA chemical peeling therapy started with a 2 weeks course of 10-15% glycolic acid daily application, then increased application up to 20-35% weekly or every second week [4]. To induce better and deeper effects one had to use in concentration up to 70% [4]. The application time until the neutralization of the pH could also be increased [4]. The glycolic acid concentration, time of application and interval between therapies could be adapted to the patient`s individual needed, deeper effect could been obtained by 20% TCA in water, TCA concentration up to 45% were also in use [4].

GA could normalized keratinization and increase epidermal and dermal hyaluronic acid and collagen gene expression. GA 70%

reduced comedo. In lower concentration GA improved both inflammation and non inflammation lessions [21]. GA improved pigmentation and diminished acne flared after the first treatment [21].

Salycilic Acid (β hydroxy acid)

It had comedolytic and keratolytic effect. Need no neutralization.17 Treated comedo and inflammation in acne, whereas SA was better than GA [21].

Jessners

Jessner`s solution was mild [17]. Jessner`s solution was contained of phenol, salicylic acid, lactic acid in ethanol. It was self neutralizing, the depth penetrance was depended on times of applied/layer [17]. Jessner`s had significant greater degree of exfoliation and reduced sebum secretion, compared with GA [21].

Baker Gordon formula (88% phenol, crotton oil).

Phenol acted as deep peels [17]. Phenol had systemic absorbtion, the side effect were cardiac arytmia, nephrotoxic. Phenol caused complete coagulation of epidermal keratin protein that blocking further penetration. Croton oil had keratolytic effect and potentiated the depth penetration of phenol [17].

Superficial Peeling

Superficial peels caused wounding to the epidermis and might reach the papillary dermis (dermal epiderrmal interface) [17,21]. Superficial peeling agent induced increasing upper dermal collagen production in response to repeated epidermal slough [19]. Superficial peels exerted their action by decreasing corneocytes adhesion and increasing dermal collagen [21]. These peels were good methods for rejuvenating the epidermis and upper dermal layers of the skin [21]. After superficial peels epidermal regeneration could been expected within 3 to 5 days and desquamated was frequently well accepted [21]. These peels were well tolerated by patients who required limitted down time after treatment [17]. Superficial peeling which were generally epidermal and pose little risk of scarring [19]. They could been used in all fitzpatrick`s skin types, skin colors and body areas [19].

Superficial peels were given in the treatment of photoaging, acne, actinic keratosis, solar lentigines and pigmentary dyschromias [17]. Given the limitted nature of the injury was induced by this peels, patients frequently needed multiple treatments on the weekly or monthly for effectiveness basis to reach a desired result [17,19]. They did not vesiculate and patient generally continue to normal activity [19]. Minimal post operative care was needed for superficial peels and patient might returned to their normal daily activity immediately, could appllied cosmetics to conceal erythema [19].

However, patients needed to be properly counceled regarding the limited benefit of superficial peels, which could not improved wrinkles and deep furrows that might been possible improved by deeper injury peels [17]. Repeated superficial peels could not produced the same result as a single deeper peels [17].

α hydroxy acids (AHA`s): Naturally occuring agents that were typically derived from foods, included glycolic acid (sugaracne) lactic acid (sour milk), malic acid (apples) and citric acid (citrus fruits). Glycolic acid had smallest moleculear size and thus greater bioavailibility that made it was the one of the most frequently applied AHAs [17]. The depth of injury was determined by the pH, concentration of the acid, amount applied and length of treatment time [17]. Glycolic acid in concentration up to 70% was frequently needed to applies for melasma, acne and photoaging Following rapid application to the entire face, it should be neutralized with sodium bicarbonat or plain water [17]. Glycolic acid had been given in combination with 5FU for the treatment of actinic keratosis [17].

Salicylic acid: Salicylic acid was β hydroxy acid, could been given in concentration of 20-30% for the treatment of acne and mild photoaging [17]. It was especially useful as an adjunctive treatment for acne because of both the keratolytic and the comedolytic properties of the salicylic acid [17]. It was also given in combination with other agents as part of Jessner`s solution [17]. Salicylic acid tended to be less inflammatory than other superficial chemical peels [17]. After application, patients experience some mild stinging and discomfort [17]. A whitening of the skin, was termed as frosting, from the precipitation of salicylic acid crystals was noted within several minutes of application [17]. Salicylic acid did not require neutralization, although cool compresses after application could sooth the skin [17].

Trichlor Acetic Acid: TCA in concentration at 10-25% was applied extensively as a superficial peel. The depth of injury was related to the concentration and the the number of application, with repeated coats of a low concentration TCA leading to greater penetration [17]. The agent was applied, and erythema and a white frost were noted within 1 minute. Patients experienced a burning sensation [17]. Handheld faned and post procedural cool compreses could reduced discomfort [17]. TCA did not require neutralization after application [17]. TCA 10-35% needed to accomplish superficial peeling on facial and non facial areas, such peel might be repeated every 7-28 days [17].

Jessner: Jessner`s solution was a combined of resorcinol, salicylic acid and lactic acid in ethanol. This superficial peel had keratolytic activity and it was typically given for acne or hyperkeratotic lessions. It was self neutralizing and multiple application could been performed to obtain a deeper injury [17].

Solid CO_2 (Dry ice): It had been given alone or in and combination with TCA to obtain a deeper peel [17]. It had been proposed as an effective treatment for acne scars and as a way to potentiate the effect of TCA to achieve a deeper peel [17].

Medium Depth Peeling

Medium depth chemical peeling was defined as a controlled wound through the epidermis and down to the deep papillary dermis [17]. In contrast to multiple treatments that were frequently performed with superficial peels, medium depth peels were generally done as single procedure because of the more significant injury produced and more robust clinical response [17]. This peels caused epidermal necrosis and dermal injury which resulted in increased collagen production during the wound healing process over the next several months [17]. Medium depth peels healing process was longer, with full epithelialization occuring in about 1 week [21]. Medium depth peeling might been repeated every 3 to 12 months based on the amount of active damage that remaining or reccuring after the peel on for continue scar effacement [19]. Medium depth peels were indicated for treatment of mild to moderate photodamaged, rhytids, pigmentary dyschromia, actinic keratosis, solar lentigines and other epidermal growth [17].

The medium depth peel was 50% TCA [17]. However it was not generally applied currently as a single agent peels because of the unpredictable results and increased incidence of scarring and dyspigmentation (hypopigmentation) [17,19]. Rather combining 35% TCA with an initial application of another agent, such as solid CO_2, jessner`s solution or glycolic acid could produced a medium depth injury (equal with 50% TCA) without the complications associated with higher concentrations of TCA alone [18,19]. As the result of the damage to the epidermis produced with the initial peel, the lower strength TCA was able to penetrate deeper and produced a more significant and even result [17]. Side effect of medium depth peeling was hyperpigmentation espescially in dark skinned patients and sun protection was recommended for several weeks after treatment [21].

Deep Peeling

Deep chemical peels were defined as those that caused an injury down to the mid reticular dermis [17]. Deep peeling caused rapid denaturization of surface keratin and other proteins in dermis and outer dermis [21]. Penetrating into the reticular dermis, the deep peels maximized the generation of new collagen.21 Epithelialization occured in 5 to 10 days, but deep peels required significant healing time, ussually 2 months or more and sun protection should been given [21].

This peels were indicated for patients with moderate to severe photodamage and advanced rhytids [17]. Deep peels produced more significant injury and patients had to extended period of postoperative healing [17]. Baker Gordon formula phenol peel was the traditional deep peel [17]. Undilluted 88% phenol did not produce a deep or consistent injury because it caused complete coagulation of epidermal keratin proteins, thus blocking further penetration [17]. The Baker Gordon formula reduced the concentration of phenol to 55%, the croton oil acted as a keratolytic and potentiated the depth of penetration of the phenol [17]. Cardiac monitoring was required because phenol could produced arrythmias [17]. Intravenous fluids were given before and during the peel to limit the serum concentration of phenol and any potential renal complications [17]. In addition, the face was divided into smaller cosmetic units, which were treated individually [17]. A 15 minutes waiting was required between treating each subunit, spreading the entire procedure over 1-2 hours, thus further limitting the systemic concentration of phenol [17]. Following application, occlusive tape could been applied if deeper wound was desired [17]. The patients were managed conservatively in the postoperative period with petrolatum and wound care until the skin was healed [17]. In addition to the cardiac and systemic concerns assosiated with deep peels, other risk included hypopigmentation, textural abnormality and scarring [17]. If any of the phenol solution accidentally contacted with the eyes, mineral oil should been given to flush, because water could potentiated the effect of the phenol [17]. Antiviral prophylactic should been administered [17].

Case Presentation

A case of very severe (4th grade) closed comedonal acne vulgaris in 16th years old stopic girl that was complicated by *Staphylococcus epidermis* foliculitis and *Pityrosporum ovale* folicullitis was reported based on anamnesis, clinical finding and laboratory examination. She got some `pimples`,erythemathous papules-pustules (less than 3 lession) and so many white head comedones (more than 100 closed comedos) on her face since 3 months before. By the time, three of the lessions were got inflammed (because of the course of the disease itself and some because of picking of the lession) and seem more erythemathous and suppurative.

She had hystory of atopic skin disease (Fufil Hanifin rajka criteria: spesific predilection at fossa poplitea, chronic reccurencies, pruritus, positive family hystory of atopy and had abnormal eosinophyl count 4,3% and upper normal limit Ig E titer).

The skin was slightly greasy but no abnormallity of serum lipid composition (normal cholesterol and triglyserides serum). No sign of clinical hyperandrogenism : no menstrual irregularity, no alopecia, no hoarse voice, no hirsutisme and the result of DHEA serum was at the upper normal limit.

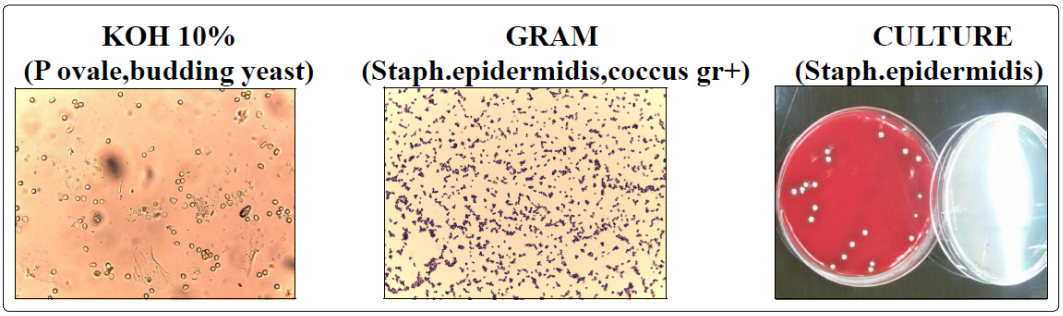
There was premenstrual dependence in acne flared up (that supported relative pores obstruction). There was genetic hystory of acne vulgaris (that supported polygenetical background in acne vulgaris). There was food dependence in acne flared up (if she took lot of saturated fatty diets). The acne lession were more severe on jilbab`s covered areas (that obstructed pores). No hystory of taking oral or topical medication (that induced acneiform eruption) before. If she felt stress, she picked 1-2 of the acne lessions on her face and it made them more inflamed. No cosmetic application and no exposure to other comedogenic substances. She did not work or live at hot and humid environment (like cooking or holiday to hot climates areas that made suddenly pores obstruction), she was a student.

The result of laboratory examinations were some abnormality. ESR 37 mm/h (Sligtly increased, supported mild acne skin inflammation process). Differential count : Basophyl 0,2% Eosinophyl 4,3% (Slightly abnormal supported atopic diagnosed), Neutrophyl 66,7%. Lymphocyte 23,2%. Monocyte 5,6% (supported acne vulgaris chronic inflammation process that activated by proinflamatory cytokine that produced by CD4+ of T lymphocytes and TLR2 of monocyte,sebocyte, macrophage and keratinocyte binding bacteria/fungi activation. In theory, hystopathology examination of the papules showed that T lymphocyte could found in early 6 hours papules, than the other cells like PMNs(neutrophyls) in 24-48 hours of papules and macrophages in 72 hours of papules).

The result of blood examinations were: IgE atopic 69,4 KIU/L(upper normal limit). Cholesterol total 170 mg/dL (middle normal level), Trigliceryde 75 mg/dL (low normal level). DHEAS 204 µg/dL (middle normal level).
Haemoglobine 13,3 g/dL, Hematocrite 40,9%, Trombocyte 321,000, Leucocyte 8.900 (Within Normal Limit)

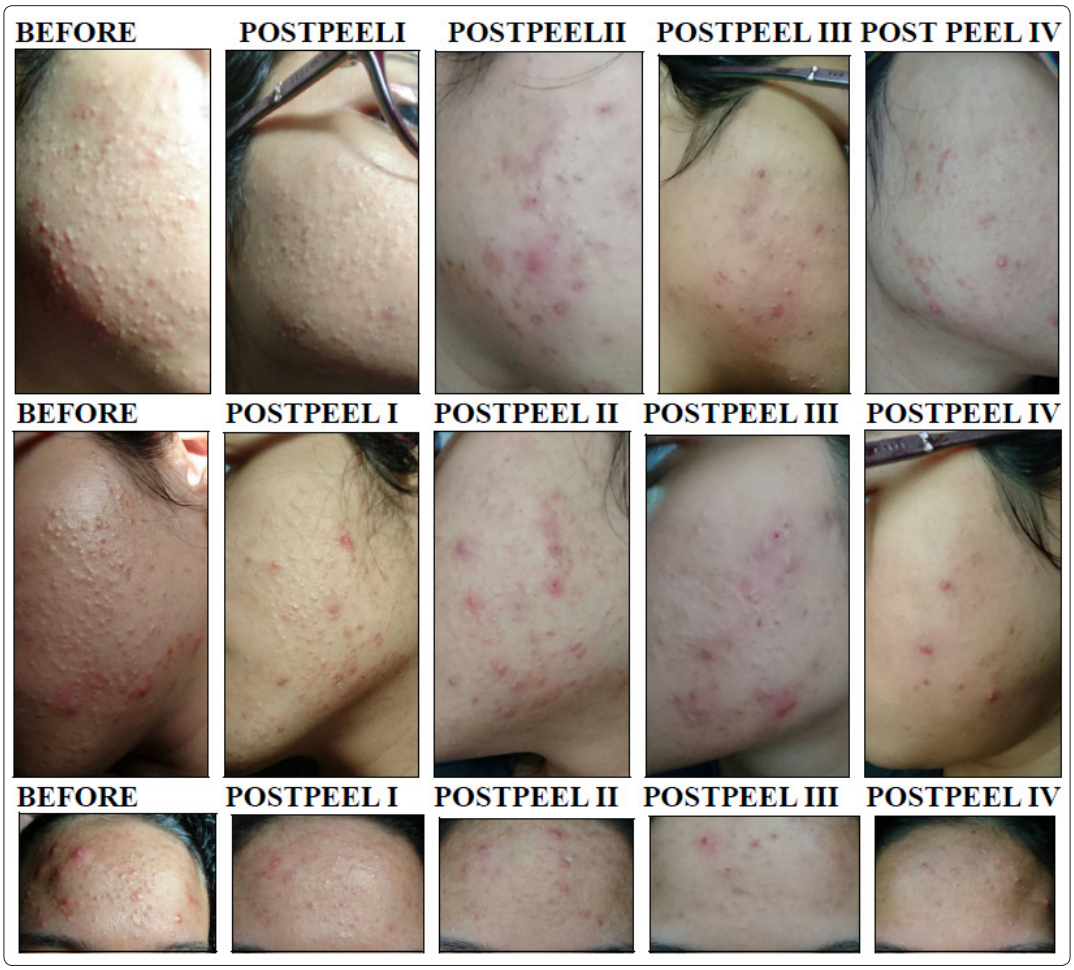
Result of laboratory examination :
Hb 13,3 g/dL (N), Hct 40,9% (N), Tr 321.000 (N), Leu 8.900 (N), ESR 37 mmHg (↑)
Ba 0,2%(N), eo 4,3%(↑), neut 66,7%(N), Lym 23,2%(↑), Mo 5,6%(N)
IgE atopy 69,4KIU/L (upper N limit)
Chol 170 mg/dL (middle N level), TG 75 mg/dL (low N level)
DHEAS 204 µg/dL (middle N level)

Direct 10% Potasium Hydroxide examination revealed positive budding yeast (supported *Pityrosporum folicullitis* complication). Gram examination revealed positive gram coccus bacteria and bacterial cultures examination revealed positive *Stapylococcus epidermidis* colony (supported *Staphylococcal* foliculitis complication). The resistance tests to antibiotics were performed and revealed resistance to cephalosporine, erytromycin,clindamycin, azytromycin, clarytromycin, gentamycin, ciprofloxacine, ofloxacine, clotrimoxazole and sensitive to doxycycline, tetracycline, minocycline, rifampicine, nitrofurantoin, linezolid,tigecyclin, vancomycin, movifloxacine.

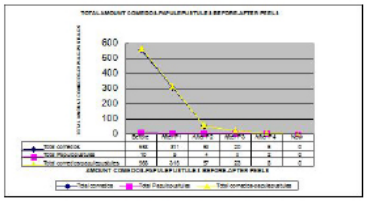


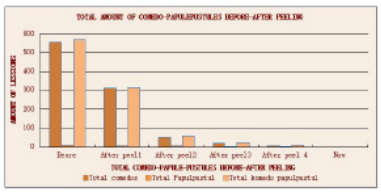
Resistance tests to antibiotic:
Resistance to cephalosporine, erytromycin, clindamycin, azytromycin, clarytromycin, gentamycin, ciprofloxacine, ofloxacine, clotrimoxazole
Sensitive to doxycycline, tetracycline, minocycline, rifampicine, nitrofurantoin, linezolid, tigecyclin, vancomycin, movifloxac$_{ine}$.

She was treated by four times 10% of TCA chemical peeling at 2 weeks intervals. Two weeks antibiotic and 10 days ketokonazole 1x200 mg were given (after the result of labolatory examinations were positive). And the result was good . There were significant improvement in clinical stage. There was decreased Cunliffe acne vulgaris grading and severity from very severe/4th grade closed comedonal acne vulgaris (more than 100 closed comedo on the face) to mild/1st grade papulopustular acne vulgaris (less than 3 papulopustular lessions on the face), diminished all of closed comedones, reduced papules-pustules and inflammation, no scar and post inflammatory hyperpigmentation were occured and no redness of the skin face.

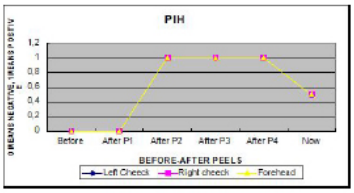


QUANTITATIVE DESCRIPTIVE STATISTICAL ANALYSIS AS CHARTS





Good descriptive clinical improvement before and after 4x 10% of TCA chemical peelings therapy in acne grading severity (decreased amount of lessions from total 568 to 8 (4th to 1st grade).

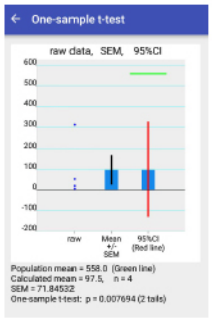


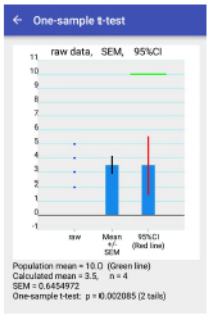
Minimal Post Inflammatory Hyperpigmentation and no scar formation were reported

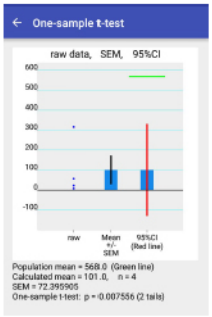
The conclusion of kuantitative descriptive statistical analysis :

- There were significant improvement before and after 4x 10% of TCA chemical peelings therapy, in acne grading severity, that were described in charts as decreased amount of comedos, papuleputules and total acne lessions according Cunliffe acne grading severity classification (from total 568 to 8 lession, 4th grade to 1st grade).
- There were some minimal post Inflammatory hyperpigmentations after 4x 10% of TCA chemical peelings therapy that was described in chart.

ONE SAMPLE tTEST







t arit=6,409603
t tab=5,840909 df=3
p=0,007694 (p value<0,01)
t arit>t tab, H0 was rejected
(+ signifficant difference in amount of comedos before-after treatment)

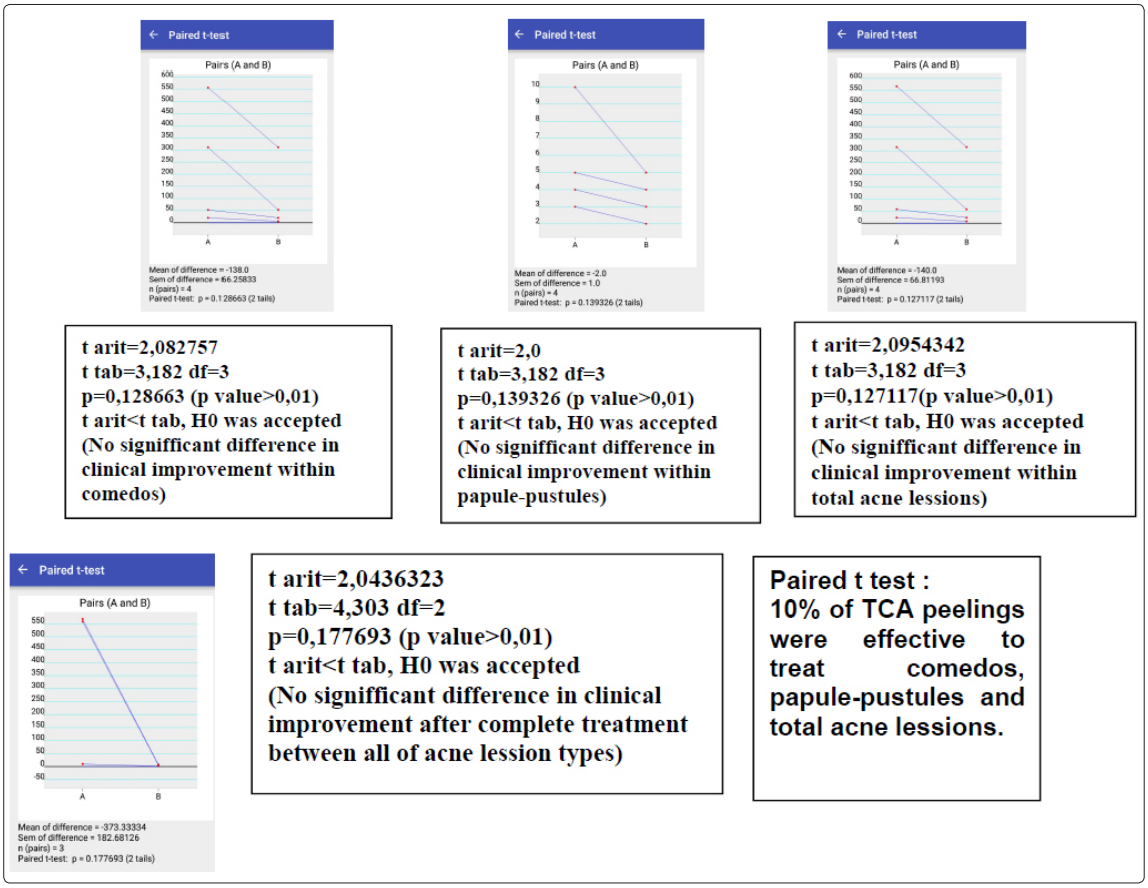
t arit=10,0697565
t tab=5,840909 df=3
p=0,002085 (p value<0,01)
t arit>t tab, H0 was rejected
(+ signifficant difference in amount of papule-pustules before-after treatment)

t arit=6,450641
t tab=5,840909 df=3
p=0,007556(p value<0,01)
t arit>t tab, H0 was rejected
(+ signifficant difference in amount of total lessions before-after treatment)

The conclusion of kuantitative inferensial parametric statistical analysis :
One sample t test conclusion :

- TCA peelings were effective to treat comedos, papule-pustules and total acne lessions. (significant different statistically in clinical improvement within comedos, papule-pustules and total acne lession type)

PAIRED t TEST BEFORE AFTER TREATMENT



The conclusion of kuantitative inferensial parametric statistical analysis :
Paired t test statistical analysis conclusion :

- TCA peelings were effective to treat both of acne lession types (comedos and papule-pustules) and also the total of acne lessions (good descriptive clinical improvement in charts). And statistically no significant different in clinical improvement, the clinical improvement was same within and between the lessions (comedo, papulepustules and total acne lessions) before and after each treatment and complete treatment.

Discussion

Comedones was the primarily lession in acne vulgaris [1]. Many closed comedos were found in this patient (clinically as very severe/4th grade closed comedonal acne vulgaris, based on Cunliffe acne grading severity classification), supported that there were follicle occlusion and hypercornification as the main important etiopathogenesis of acne vulgaris in this pubertal patient [1-4].

There were decreased incidence of acne vulgaris in atopic dermatitis patients that had low sebum excretion [3]. This patient was also diagnosed as atopic dermatitis (fulfil Hanifin Rajka criteria : spesific predilection at fossa poplitea, chronic reccurencies, pruritus, positive family hystory of atopy and there were elevation eosinophyl count (4,3%) and upper normal limit IgE atopy). So it was a rare case.

Lipid composition of skin surfaces acne patient was contained triglyserides, free fatty acids, wax esther, squalene, cholesterol, cholesterol ester [4]. The skin of this patient was greasy but the result of cholesterol and triglyserides serum were normal. The skin was greasy might been caused by free fatty acids. (abundantly bacteria-*Staphylococcus epidermidis* and fungal-*Pityrosporum ovale* were found on cultures and direct examination produced lipase that hydrolized triglyceride to free fatty acids that than flourished bacterial and fungal growth themselves)Bacteria and *P.ovale* were bound to T lymphocytes/ keratinocytes/ macrophages/ monocytes/ sebocytes released cytokine pro inflammatory mediators that induced inflammation process [3,4,6]. In this patient some lession got inflammed because of *Staphylococcus epidermidis* and *Pityrosporum ovale* complication as secondary infection that induced pro inflammatory cytokine released and marked inflammation processes.

Active sebaceous glands were required for the development of acne vulgaris.3 Sebaceous activity was predominantly dependent on androgen of gonadal and adrenal origin [3]. Androgen hormones also had pro inflammatory effect [4]. In the normal level of androgen production, there were increased stimulation of sebum production in sebaceous gland of acne vulgaris patient [1]. There was possibility an end organ hyper response of the sebaceous glands to normal circulating levels of hormones [4]. Acne vulgaris patient extend on average more sebum than normal subject, the level of secretion correlated with the severity of acne [3]. But in 24% acne vulgaris

patient had no hormonal abnormality [3].

In this patient the result of hormonal examination DHEAS was normal. So in this patient there were increased sebum activation to normal hormonal changing (might been there was an end organ hyper response of the sebaceous glands to normal circulating levels of hormones because acne lessions were appeared only on her face and there was no acne on the other part of her body) and still supported the role of sebum in acne vulgaris etiopathogenesis.

About 70% of women were complaint of a flare 2-7 days pre menstrually, related to premenstrual change in hydration of pilocebaceous epithelium, progesterone and estrogen [3]. Pilocebaseous duct orifice was smallest in 16-20th day of the menstrual cycle, reduced the flowed of sebum, produced relative obstruction and increased pro inflamatory cytokine mediators to concentrate in the sebaceous gland/duct lumen and stimulated premenstrual acne flared up [4]. Estrogen might reduced SHBG levels, so there was increased of free testosteron level thus increased sebum production [3,4]. There was premenstrually flare up of acne vulgaris in this patient.

Acne was polymorphous dermatosis with a polygenetic background, did not follow Mendelian rules [4]. Several studies had shown that genetic factors influenced susceptibility in acne (there were 45% acne parents`s in schoolboys acne patient in Germany and genetic role in acne was also supported by genetic study in twins) [3,4]. But the exogenous also factor influenced the severity of disease inflammation process (bacterial colonization, hot humid environment,etc) [4].

There was family hystory of acne in this patient (brother`s and sister`s both of her parent).
A personal study of 100 acne patients found no link between acne severity, calory intake, carbohydrate, lipid, proteins, minerals, amino acid or vitamins. Food had no significant influence in acne vulgaris [3,4]. Rooks said that overall there were no correlation between acne and food [4].

But Andrews reported that high glycemic food aggravated acne [2]. Chocholates, caramels and fatty acids were accused of aggravating acne [4]. Chocholate had insuline like substance [2]. In high insulin levels, there were low SHBG levels and high free testosterone levels that increased sebum production.. In some study showed that rich fish diets people had less acne than more saturated fat diets people [4]. The possible effect of nutrition on the age of puberty might been relevant, as acne was more likely after the started of sexual development and occured when the body weight attained about 48 kg [3]. Diets with marked weight loss improved acne.4 But Crash diets combined with strong physical stress increased androgen release [4].

This patient had food influence in acne flared up, The acnes were more and severe when she took lot of saturated fatty diets and firstly acne occured in her puberty age (16^{th}) with marked sexual development and her body weight attained to 48 kg.

The acne lession appeared more on areas that covered by jilbab, supporting that ductal hydration and relative obstruction (sweating, humid environment) were the responsible factor [3]. UVA radiation enhanced the comedogenicity of sebum (convert squalene into squalene peroxidase which enhanced comedogenesis) Some kind of UV beneficial in acne treatment (in photodynamic therapy) [3,4]. The wavelength 400-450nm light activated *P acnes* porpyrins that destroyed *P acnes* in the follicle themselves [4]. Visible light (blue and red) had antimicrobial activity [4]. Erythemathous and suberythemathous dose UVB made tanning and scaling of the interfollicular epidermis and helped desquamate corneocyte from around acroinfundibulum Acne lession in this patient also found on open areas that exposed to sunlight [4].

In this patient, acne itself induced stress and picking acne aggravated the appearance in some lessions.3 Some cosmetic were occlusive and comedogenic but there was no cosmetic application in this patient [3]. Some topical and oral drugs were acne induced but no topical and oral medication that she got before [3,4].

In theory, hystopathology examination of the papules showed that T lymphocyte could be found in early 6 hours papules, than the other cells like PMNs(neutrophyls) and CD4+ T ;ymphocytes in 24-48 hours of papules and CD4+ T lymphocytes, macrophages and giant cells in 72 hours of papules [4].

In this patient, the result of blood laboratory examination were some abnormality. ESR 37 mm/h Leucocyte 8.900 (slightly elevated but no fever, supported mild acne papules-pustules inflammation process). In differential count : Eosinophyl 4,3% (Slightly abnormal supported atopic diagnosed), Neutrophyl 66,7%. Lymphocyte 23,2%. Monocyte 5,6% (supported acne vulgaris inflammation process that activated by pro inflammatory cytokine that produced by T lymphocytes, monocyte, sebocyte, macrophage, keratinocyte binding bacteria and fungi activation).

There was a little or no relationship between the number of bacteria on the skin surface or in the duct and the severity of acne Sebum excretion rate and ductal cornification correlated well with clinical severity [3]. The three major organisms were isolated from the surface of the skin and the duct of patients with acne were *Propinibacterium acnes*, *Staphylococcus epidermidis* and *Malassezia furfur* [3]. *Staphylococci* were the first organism that colonized the normal skin people [4]. Acne was not infectious [3]. In this patient, the result of direct KOH 10% examination showed budding yeast+ that supported *Pityrosporum ovale* foliculitis complication. The result of direct gram examination and blood agar cultured revealed coccus possitive gram bacteria that supported Staphylococcus epidermidis folliculitis complication. The acne lessions of this case were complicated by *Staphylococcus epidermidis and Pitirosporum ovale* and there were microbial flora abnormality [3,4]. that supported one of the acne vulgaris etiopathogenesis in this patient. Actually there were no *Propionibaxterium acnes* were found (in gram examination revealed no positive rods gram bacteria and in direct examination revealed no non motile positive gram rods bacteria), The resistance tests to antibiotics were performed and revealed that *Staphylococcus epidermidis* was resistance to cephalosporine, erytromycin, clindamycin, azytromycin, clarytromycin, gentamycin, ciprofloxacine, ofloxacine, clotrimoxazole and sensitive to doxycycline, tetracycline, minocycline, rifampicine, nitrofurantoin, linezolid, tigecyclin, vancomycin, movifloxacine.

Staphylococcus epidermidis were found as comensal (normal colony at nares, head and axilla) and patogen (as chronic nosocomial infection that infected through contaminated stuff in cardiac cathetherization or other procedures). It was difficult to be eradicated, it had high

resistances, it was easy to be infected again after it was treated (by hands or contaminated stuff) and it was clinically found as chronic infection. But this colonization inhibited *Staphylococcus aureus* virulencies, *Staphylococcus epidermidis* was the first normal flora on the skin surface [4,7].

Pityrosporum ovale was lipophilic, saprophytic, budding, unipolar, dimorphic gram positive, double walled, oval to round yeast. They were normal part of the follicular skin flora, and alteration in flora caused uncontroled growth of yeasts and would been pathogenic [4]. They needed free fatty acid for survival (they had lipase that hydrolized triglyceride to free fatty acid). They were found in stratum corneum and in pilar follicles in areas with increased sebaceous gland activity such as chest and back [8].

So the anamnesis, clinical finding and labotatory examinations supported the diagnosed as very severe (4th grade) closed comedonal acne vulgaris that was complicated by Staphylococcus epidermidis and Pityrosporum ovale foliculitis in atopic hystory 16th years old girl patient.

Chemical peeling/chemical resurfacing/chemoexfoliation/ chemosurgery involved an application of one or more exfoliating agents to the skin, resulting in the destruction of portion of the epidermis and/or dermis with subsequent regeneration. This produced controling wound and reepithelialization [19].

TCA 10% was superficial chemical peeling, considered as adjunctive therapy in acne, frequently added to first line therapy such as retinoids and antibiotic, and as first line therapy for acne scar and skin rejuvenation [19]. In high concentration was good for treating acne scar (CROSS/ Chemical reconstruction of Skin Scars technique) [18-20]. TCA was cheap and save because no systemic absorbtion, but it felt pain (more than SA,less severe than phenol). Chemical peeling had keratolytic effect by dissolved intercellular cement and reduced corneocyte adhesion, anti inflammatory effect by commedolytic action (Salisilic Acid peels better) and bactericidal action (Glycolic acid better) in acne vulgaris [20].

TCA chemical peeling caused epidermal coagulation and collagen necrosis up to the upper reticular dermis, reepithelialization begun from survival islets of keratinocytes and skin appendages and the clinical effect were due to resultant increased in dermal volume of collagen, glycosaminoglycans and elastin [17,19,20]. Keratolitic and comedolitic effect of TCA diminished hypercornification-ductal obstruction and bacterial-fungal colonization, so decreased inflammation and free fatty acid that was important for bacteria and fungal growth, so it acted as antibiotic and antifungal adjunctive therapy and could be combined with antibiotic and antifungal and solved resistance problems to antibiotic and antifungal in acne therapy.

Conclusion

TCA 10% was superficial chemical peeling, considered as adjunctive therapy to the first line acne therapy retinoids and antibiotic, and TCA was the first line therapy for acne scar and skin rejuvenation.TCA was cheap and save because no systemic absorbtion, had keratolytic effect (comedolytic action) and anti inflammatory effect (bactericidal action). It could be combined to antibiotics and antifungal therapy and solved resistance problems to antibiotic and antifungal in acne therapy.

In this case 4x 10%TCA chemical peeling in 2 weeks intervals showed good result for treating very severe (4th grade) commedonal acne vulgaris without scars formation and revealed no post inflamatory hyperpigmentation. There were diminished of all closed comedos on her face.

There was decreased severity from very severe (4th grade) comedonal acne (more than 100 closed comedos on the face) to mild (1st grade) papulopustular acne vulgaris (only 3 papulopustular acne lession on her face). TCA was good in comedolytic activity. And topical therapy with retinoid 0,025% to supress comedo formation and maintain therapy was chosen up to now.

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