Annual Scientific Meeting of Dermatology & Venereology 2000

reported by Dr. L. S. Ku and Dr. T. Y. Ho

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Organizer:	HKSDV

Soft Tissue Tumours in Dermatological Practice

Speaker: Dr. E. Calonje

The field of cutaneous mesenchymal tumour has always been an obscure subject in the training of clinical dermatologists. There are over 100 soft tissue tumours and majority of them are very rare. They often lack clinical features that will allow a diagnosis to be made on clinical grounds alone. Histological diagnosis is therefore often required. All these account for the lack of interest in this field. The following are however a few points that the clinicians should know:

Soft tissue tumour associated with syndromes

The association between von Recklinghausen's disease and the presence of multiple cutaneous neurofibroma is a well-known example. Mucosal neuromas present as multiple lesions in the oral cavity and are associated with multiple endocrine neoplasia syndrome type IIb or *Sipple syndrome*. This is an autosomal dominant condition associated with medullary carcinoma of the thyroid and phaeochromocytoma.

Cowden's disease very often presents with multiple tricholemmoma, acral keratoses, palmar pits and oral fibromas. Dermal fibroma is characteristic but not specific of the disease. The presence of multiple fibromas should raise the possibility of Cowden's disease which is often associated with breast (up to 50% of the female patients with the disease) and thyroid carcinoma.

Carney complex, an autosomal dominant disease, consists of cutaneous, cardiac and mammary myxomas, multiple lentigines (cutaneous and mucocutaneous), blue naevus and endocrine overactivity (Cushing's syndrome, sexual precocity and acromegaly) and rarely psammomatous melanotic Schwannoma. Early diagnosis based on the cutaneous signs is important because the underlying cardiac myxomas may cause fatal embolism.

Benign cutaneous soft tissue tumours that can simulate malignancy clinically or histologically

Fibrous histiocytoma (*dermatofibroma*) (FH) can attain a large size or occurs in unusual sites such as the fingers and toes with ulceration. This can lead to an erroneous diagnosis such as deramtofibrosarcoma protuberans or other sarcomas. Histologically, the cellular variant of FH and the aneurysmal benign variant may be diagnosed incorrectly as malignant. The cellular variant of FH is usually larger than 1 cm with ulceration and may present at atypical sites, for example, face, hands and feet. Histologically, there is a prominent fasicular pattern, less polymorphism, deeper involvement of the subcutis with necrosis and a high mitotic rates. This may lead to a misdiagnosis of leiomyosarcoma or dermatofibrosarcoma protuberans. Aneurysmal benign variant of FH shows extensive bleeding with formation of pseudovascular spaces. They often increase in size rapidly and tend to be cellular with a higher mitotic count. Their behavior is, however, benign. The recurrence rate is around 20%.

Two further histological variants of FH with no distinct clinical features may also be a potential problem for diagnosis. 1) Pseudosarcomatous or atypical FH: it may be misdiagnosed histologically as atypical fibroxanthoma or a type of sarcoma. 2) Clear cell FH: the clear cells may obscure the typical background changes and a misdiagnosis of a metastatic tumour with clear cell changes may be made. This can be avoided by noting the absence of cellular atypia and the results of appropriate immunohistochemical stains.

Nodular fasciitis is a reactive myofibroblastic proliferation presenting as a rapidly growing subcutaneous lesion in the limbs of young patients. The rapid clinical growth and cytological atypia and frequent mitotic figures can lead to a misdiagnosis of malignancy. Simple excision is the treatment of choice.

Kaposi's sarcoma (KS) is a low-grade malignant vascular tumour that present in well-defined groups of individuals (HIV-related KS, immunosuppression related KS, endemic Mediterranean KS and African KS). Recent researches suggested that it may represent a reactive process in which Human Herpes virus 8 might have a pathogenic role. Clinicopathological correlation to establish a diagnosis of KS is very important. Histological diagnosis of early patch stage KS is often very difficult. Many benign tumour and reactive conditions like tufted angioma, stasis dermatitis and spindle cell haemangioma may be misdiagnosed as KS.

Low-grade malignant or malignant soft tissue tumours often associated with high morbidity or mortality

The concept of low grade or borderline malignancy refers to tumour with a variable rate of local recurrence and a low but definite risk of metastasis. It also refers to tumour in which it is difficult to predict clinical behavior accurately based on histological appearances.

Dermatofibrosarcoma protuberan (DFSP) is a prototype. The local recurrence rate is up to 58% unless wide excision is performed. The metastatic rate is 1%. On the other hand, the metastatic rate of fibrosarcomatous variant of DFSP is almost 15% and its accurate diagnosis is thus important prognostically. Histological diagnosis of DFSP can be confused with neurofibroma or FH and hence may result in serious mismanagement. It is important to remember that *not* all multinodular cutaneous soft tissue lesions represent DFSP as variant of FH can rarely attain a very large size.

Atypical fibroxanthoma (AFX) typically arises as a rapidly growing tumour in sun-damaged skin of elderly males. There is a low rate of local recurrence and a negligible metastatic rate despite the alarming clinical appearance and histological features. AFX is a diagnosis by exclusion after spindle cell melanoma, spindle cell squamous cell carcinoma and leiomyosarcoma have been ruled out by immunohistochemical stains.

The top four malignant soft tissue tumours affecting the skin are 1) leiomyosarcoma, 2) angiosarcoma, 3) myxofibrosarcoma and 4) epithelioid sarcoma.

Cutaneous leiomyosarcoma, being fairly uncommon, presents mainly in the limbs of young adults, particularly males. It is often painful. The local recurrence rate is high if not excised completely but the metastatic rate is almost non-existent.

Cutaneous angiosarcoma (AS) occurs in 1) face and scalp of elderly patients; 2) as a late complication of irradiation therapy; 3) secondary to long-standing lymphoedema of any causes (Stewart-Treves syndrome). The histological diagnosis of AS is usually not difficult except in small biopsies or in poorly differentiated tumours. Immunohistochemistry might be required to confirm the diagnosis of the latter. The prognosis is very poor with a five-year survival rate of 12%. Response to radiotherapy and chemotherapy is poor, the only chance to improve survival is early surgical treatment.

Myxofibrosarcoma (MFS) occurs mainly in the subcutaneous tissue (up to 60%) of middle aged patients. This tumour shows a spectrum of histological appearances based on cellularity, degree of cytological atypia and degree of myoid change. High-grade lesions are very cellular and pleomorphic. They show only focal myxoid change and have a tendency to spread to lymph nodes. Low grade lesions have a high local recurrence rate but a low metastatic rate. Adequate excision is of paramount importance because recurrent tumours may progress to a higher grade. The overall five year survival is around 60%.

Epithelioid sarcoma, a highly malignant rare tumour of uncertain histogenesis, presents mainly in adolescents and young adults with a predilection to male. Spreading through neurovascular bundles and fascial planes, they often have a sporotrichoid distribution. Thus, an infective process may be confused clinically. The immunohistochemical profile of this tumour is very useful to confirm the diagnosis. The five year survival rate is up to 50% but most of the patients eventually died of distant metastasis.

Learning points:

Histological diagnosis of dermatofibrosarcoma protuberan can be confused with neurofibroma or fibrous histiocytoma and hence may result in serious mis-management

Contact Dermatitis in Hong Kong

Speaker: Dr. T. Y. Lee

Diagnosis and management of contact dermatitis

Proper management of contact dermatitis consists of 1) symptomatic treatment of dermatitis, 2) identification of the allergen/irritant and 3) counselling. The most challenging part is the accurate identification of the causative agent.

Irritant contact dermatitis

The etiological diagnosis is mainly circumstantial. Skin patch test plays little role in the confirmation.

Allergic contact dermatitis

A detailed and accurate history is most important in establishing the etiological diagnosis. Skin patch test or provocative use test are sometimes useful.

Phototoxic and photoallergic reactions

The diagnosis of an allergic photocontact dermatitis is made by patch and photopatch testing. When a phototoxic contact reaction is evident, testing is not usually indicated.

Common causative agents of contact dermatitis in Hong Kong

The speaker conducted a study in 1987-1988 on the prevalence and etiological factors of contact dermatitis in Hong Kong. It was found that the most common causative agents were soap or detergents (22.0%), followed by traditional Chinese medicine (17.3%), metals (13.4%), cosmetic (11.6%) and western medicine (9.0%). In 10.8% of the patients, the causative agents were not well-defined though contact dermatitis was strongly suspected clinically.

The pattern of reactions to the European standard allergens are remarkably similar in four Asian cities namely Beijing, Taipei, Singapore and Hong Kong. The top five common allergens are fragrance mix, nickel sulphate, cobalt chloride, balsam of Peru and neomycin sulphate, with some difference in ranking positions.

Fragrance mix ranked first in Hong Kong (19.5%) but fifth in Beijing (8.7%), the difference is probably due to the low usage of cosmetics in the latter. With the open-door policy and improving economy in China, the trend is however changing.

Nickel was the most common allergen in Beijing, Taipei and Singapore, but was only ranked second in Hong Kong (16.4%), probably due to the more common use of pure gold and platinum here.

Cobalt ranked third in Hong Kong (11.3%) but was much lower in Singapore (4.5%).

Chromium allergy was very common in Beijing (17.4%) but not in Hong Kong (1.6%). Cement was a common source of chromium. The low prevalence in Hong Kong might be due to the addition of ferrous sulphate to cement or due to mechanization of the building process.

Neomycin, being a popular and easily available medicament for self-medication, was the most common medication in the European Standard Allergen to cause allergy in Hong Kong.

Bone-setter's herbs dermatitis

In Hong Kong, bone-setter's herbs dermatitis is the most common cause of dermatitis around joints. In 1991 the speaker reported the symptoms, natural progression, skin biopsy findings, patch test results and treatment response of 20 such patients. Ten patients were patch tested and all showed positive reactions to bone setter's herb. The tests were negative in another 20 patients having eczema but not herb related contact dermatitis. Moreover, the latent period tended to shorten on repeated exposure. Thus, the reaction appeared to be allergic rather than irritant. Topical corticosteroid alone was inadequate in most cases for control. Systemic prednisolone 20-40 mg daily was recommended by the speaker right from the start of the treatment. *Myrrh*, as indicated from the speaker's studies, is a common allergen in bone setter's herbs dermatitis.

A new form of garlic dermatitis in Hong Kong

Contact dermatitis due to garlic classically occurs in the finger tips of food handlers and housewives. In Hong Kong, since many Chinese believe that garlic has antifungal and antibacterial activities, a new form of contact dermatitis occurs. The speaker described eight patients who developed dermatitis after applying garlic as topical medicament for skin diseases. Control study by various tests showed that the clinical reactions were due to irritation rather than to allergy.

Prevention of contact dermatitis in Hong Kong

This includes identification of potent irritants and allergens and hence prevention of and protection against their exposure. Improvement of personal and environmental hygiene, health education, pre-employment and periodic health screening are also important.

Patch testing

This is underperformed in Hong Kong due to the inertia of practicing physicians. The reasons behind might be the hot and humid climate in Hong Kong as well as the failure to realize that patch test can help to identify the allergen and subsequently lead to a "cure" for the problem. Education to overcome the inertia and correction of the misconception is thus the logical approach.

Standard battery of allergens for Hong Kong

The aim is to establish a standard battery which will include most of the allergens commonly encountered in Hong Kong and which can be used for screening purposes.

Traditional Chinese medicine

All proprietary traditional Chinese medicine should have their detailed formulae and side effects listed. The use of potentially dangerous herbs which are potent irritants or allergens should be restricted.

Learning points:

Patch testing is very much under-performed in Hong Kong. Physicians should realize that by identifying the allergens or irritants and avoiding them, one can offer a "cure" to patients with contact dermatitis.

High Prevalence of Foot Diseases in Europe: Results of Achilles Project

Speaker: Prof. D. Abeck

The Achilles Project was initiated to collect information on the prevalence of foot diseases and their predisposing factors. The project consisted of two parts: a survey consisting of a clinical examination of the feet by general practitioners; and a study with a mycological examination if an infection of the feet was suspected by dermatologists.

Initial data collected from 16 European countries showed that 57% of the 70,497 patients recruited in the survey had one or more foot diseases; whereas 61.3% of the 19,588 patients recruited in the study was affected similarly. The prevalence of fungal foot disease was 34.9% and 40.6% in the survey and in the study respectively, whereas that for non-fungal foot disease was 38.4% and 41.7%. Increasing age increased the risk of having a foot disease. Orthopaedic conditions and metatarsal corns accounted for the majority of the non-fungal foot diseases, while onychomycosis and tinea pedis were the leading causes for fungal conditions with Trichophyton species responsible for 75.1% for culture-proven cases. 3,220 subjects had toenail infections, 1,766 had a mycotic skin infection and 876 had a combined infection of toenails and skin.

The prevalence of foot diseases reported within the Achilles project, with examination of more than 90,000 patients, was higher than those reported from smaller studies. As foot diseases can severely interfere with daily activities and the quality of life. Knowledge about predisposing factors can help to keep feet healthy.

Learning points:

The prevalence of fungal foot disease in 16 European countries ranged from 34.9-40.6% in the Achilles project.

Laser Surgery in the Chinese

Speaker: Dr. H. H. L. Chan

Laser surgery in Chinese has two important differences from that in the Caucasian. Firstly, certain conditions are more commonly seen in Asians. Secondly, the higher epidermal melanin content in Asian's skin makes adverse reaction more likely after laser surgery. Laser therapy for Naevus of Ota, which is commonly seen among the Asian race, can help illustrate the above.

Q-switched ruby laser (QS Ruby) had previously been shown to be useful in the treatment of Naeus of Ota. However, the usefulness of Q-switched Alexandrite (QS Alex) and Q-switched Yittrium-Aluminium-Garnet (QS Nd-YAG) had not yet been established by larger scale studies. Studies were done recently in Hong Kong to address this problem.

Regarding to short-term complications in the treatment of Naevus of Ota, QS Alex was shown to be better tolerated than QS Nd-YAG. For long-term complications, 171 patients who had been treated with QS Alex, QS Nd-YAG, or a combination of both were interviewed and examined. Of the total 211 treatment sites, 15.3% had hypopigmentation, 2.9% had hyperpigmentation, and 2.9% and 1.9% had texture changes and scarring respectively. The combined treatment group was associated with a significantly higher risk of complications. Recurrence of Naevus of Ota after complete or near complete clearance with laser treatment, which had not been reported before, was found in 13 patients. This is an important issue and should be considered especially when treating children.

Regarding the long-term complications of QS Ruby in the treatment of Naevus of Ota, a similar study was carried out in liaison with a Japanese university. Of the total 101 patients assessed, hypopigmentation was the most common complication, affecting 16.8% the patients; 5.9% had hyperpigmentation and one patient had infection during the course of treatment. One patient who had complete clearance developed recurrence.

To compare the clinical efficacy of QS Alex and QS 1064 Nd-YAG, 40 patients with Naevus of Ota were studied prospectively. All had received at least three treatment sessions with half of the lesion treated by QS Alex and the other half by QS 1064 Nd-YAG. It was concluded that QS 1064 Nd-YAG was more effective than QS Alex in producing lightening of the lesion.

Learning points:

Recurrence of Naevus of Ota after complete or near complete clearance with laser treatment is an important issue and should be considered especially when treating children.

Dermatology Surgery

Speaker: Dr. M. K. Tung

The first clinical visit is important to establish good rapport with the patient. Wrong concepts and unrealistic expectations should be corrected. A good history, physical examination and psychological assessment are all important. Enquiring about drug sensitivity, examination of all scars, and taking clinical photos should be remembered.

Preoperative preparations include correction of nutritional deficiencies, improving all medical problems, treatment of local conditions, advising the patient to stop smoking for two weeks prior to operation, preparation of the operation area (e.g. shaving as appropriate), and pre-operative antibiotic if indicated.

The doctor should be familiarized with the Langer's lines or the relaxed skin tension lines, and the important structures underneath the pathology. A magnifying loop is helpful but not essential; however, the doctor should ensure that any visual deficit of his or her own had been corrected. The nurse should be competent as regarding to sterilisation procedures and operation assistance techniques. The operation theatre should have adequate lighting, an adjustable operation table, and availability of the diathermy machine and resuscitation trolley.

Concerning operation techniques, it is important not to use alcoholic antiseptic for the operation field to prevent burn injury from diathermy. The resultant scar should be as parallel to the relaxed skin tension lines as possible, and the incision lines should be marked with Gentian violet. The use of adrenaline in local anaesthetics should be avoided in end organs like the digits and the penis. To optimise the appearance of the scar, the most superficial layer should be closed with

non-absorbable suture unless it is the mucosa. Adequate haemostasis is important to prevent haematoma formation. Wound healing may be improved by the following: 1) exposure of the sutured site wherever possible, 2) use of chloramphenical ointment, 3) use of systemic antibiotic when the wound is big, 4) stopping smoking, 5) avoiding direct ultraviolet light on the wound, and 6) avoiding ingestion of "Snake Head Fish". The patient can be reassured that the scar will continue to improve for six to nine months for Chinese.

Common Pitfalls in Dermatopathology with Clinical Correlation

reported by Dr. Y. P. Fung

Date:	7 July, 2000
Venue:	Hotel Miramar, Hong Kong
Speaker:	Dr. E. Calonje
Organizer:	HKSDV; Scientific Meeting

Dr. Edwardo Calonje shared his valuable experience on pitfalls in dermatology and dermatopathology through case discussions. The patients described were often misdiagnosed for many years. Table 1 and 2 summarize the potential sources of diagnostic error by the dermatologist and dermatopathologist respectively.

Two non-Caucasian patients with progressive patches of hypopigmentation were discussed. They were both misdiagnosed initially as having post-inflammatory hypopigmentation. Leprosy was considered in both cases as differential diagnosis. After multiple skin biopsies, it was subsequently revealed that one suffered from **hypopigmented mycosis fungoides** while the other suffered from **post kala-aza dermal leishmaniasis**. While hypopigmented mycosis fungoides is rare in Caucasians, it is sometimes seen in black patients. Post kala-aza leishmaniasis is an unusual complication of visceral leishmaniasis. Seen in India, North and Eastern Africa, this is often confused with leprosy. Patients typically present with multiple hypopigmented macules, papules, plaques and nodules. The time of presentation after kala-aza varies and patient may not give a history of previous infection. The presence of Leishman-Donovan bodies in histiocytes is diagnostic.

Table 1. Pitfalls in dermatology

1. Inadequate clinical history
2. Inadequate clinical examination
3. Unusual presentation of relatively common conditions
4. Rare condition unknown to clinician

Table 2. Pitfalls in dermatopathology

1. Inadequate tissue sampling
2. Artifacts
3. Biopsy not representative of clinical condition
4. Failure to perform serial section
5. Subtle histological changes
6. Lack of close clinico-pathological correlation
7. Lack of adequate clinical data

Skin biopsy from a febrile patient with a rapidly enlarging ulcer claimed to have occurred after an insect bite was performed. The provisional clinical diagnosis was insect bite reaction. Histology was however incompatible showing patchy hemorrhagic mixed infiltrate and edematous dermis. Patient then developed acute renal failure and jaundice. Direct questioning revealed that the patient worked for a leather firm one week before the onset of symptoms. Microscopy of the blood film from blood culture showed large Gram-positive bacillus and **cutaneous anthrax** was subsequently diagnosed. Caused by bacillus anthracis, a gram-positive bacillus (6-10 um long), anthrax is rare in Europe and USA. Ninety-five percent is due to primary inoculation by contact with infected animals or their product while the remaining 5% was from inhalation. If untreated, the mortality is up to 20%. This case illustrates the importance of careful history and clinico-pathological correlation.

A 5-year-old boy on multiple anti-convulsants developed pink macular lesions with blistering on his right elbow. A skin biopsy was performed to confirm

the provisional diagnosis of fixed drug eruption (FDE). Histology showed neither hydropic degeneration nor lichenoid infiltrate typically seen in FDE. Subtle changes identified as sweat gland necrosis was seen in the dermis. The findings overturned FDE and the diagnosis of **bullae and sweat gland necrosis in drug-induced coma** was made. This unusual condition is mainly but not exclusively seen in comatose patients. This was illustrated in our patient who was not comatous. It may result from carbon monoxide poisoning, barbiturate overdose or severe illness from other causes. It is thought to be due to ischemia induced by pressure and toxic effect of drugs. Overdose of anti-convulsants was thought to be responsible in the case.

A patient developed indurated, waxy and slowly enlarging peri-orbital swellings for months. This was biopsied and the clinical provisional diagnosis was chronic angioedema. Histology showed a different picture. In the superficial and deep dermis, there were extensive deposition both intracellularly and extracellularly of what seemed to be an amorphous eosinophilic material on low-powered examination. High power examination revealed numerous eosinophilic rhomboidal, rectangular, and needle-shaped crystals of different sizes. Many of the crystals were in the cytoplasm of histiocytes, but there was also extensive deposition in the interstitium. Electron microscopy showed intracellular and extracellular rectangular rhomboidal crystals of variable size. Bone marrow examination confirmed the diagnosis of multiple myeloma. **Cutaneous crystal storing histiocytosis** was a rare presentation of multiple myeloma but crystal deposition in myeloma was often seen at autopsy with the kidney and cornea being most commonly affected. Treatment of myeloma led to regression of the cutaneous swellings but the patient died of other complications from myeloma.

A man presented with an asymptomatic solitary oval patch of poikiloderma (atrophy, pigmentation and telangiectasia) at his left shoulder. There was no lesion anywhere else. This was biopsied to exclude unilesional mycosis fungoides. Histology was reported as "some stages of poikiloderma and no evidence of mycosis fungoides". Careful clinical history and clinical correlation later revealed that the patient received cardiac catheterization under fluoroscopic guidance one year before the rash. The site of the lesion coincided with that of the X-ray tube. Thus the correct diagnosis was **chronic radiodermatitis following cardiac catheterization**. This case stresses the importance of clinical history in making the diagnosis.

A woman was investigated for pemphigus vulgaris. She developed erosive vulval eruption for four years refractory to all forms of topical steroid and anti-fungal cream. The lesions had a serpiginous border and there were few pustules at the advancing edge. Histology showed psoriasiform hyperplasia, oedema and subcorneal pustules. Superficial epidermal necrosis was also noted. The differential diagnoses included pellagra, acrodermatitis enteropathica and necrolytic migratory erythema (NME). Blood test showed high serum glycogen and the patient was diagnosed to have **necrolytic migratory erythema secondary to underlying glucagonoma**. Patients with NME typically present with annular or serpiginous scaly red papules and plaques at the body folds. They may also have glossitis, stomatitis, diabetes, weight loss and deep vein thrombosis. Not all cases are associated with glucagonoma. The eruption is thought to be linked with amino-acid deficiency.

The entity of **lichen planus-like keratosis** was also discussed. This fairly common condition is often unrecognized. Considered by most as a distinct lesion, it shares morphological features of lichen planus and lichenoid actinic keratosis. Mostly found in elderly patients at the upper and lower limbs, it is described to evolve from solar lentigo. Lichen planus-like keratosis typically shows lichenoid lymphocytic infiltrate with hyperkeratosis, hypergranulosis, focal acanthosis, and focal parakeratosis, without prominent atypia of keratinocytes. Atypia is present in lichenoid actinic keratosis.

A patient with **lichen planus pemphigoides** was presented. She had lesions clinically resembling lichen planus but also developed blisters away from lichen planus lesions. Histology showed features of lichen planus but "too many eosinophils". This rare condition is thought to be unique rather than merely a coexistence of lichen planus and bullous pemphigoid. While direct immunoflorescence shows linear deposition of IgG and C3 at the dermal-epidermal junction, circulating IgG autoantibodies react to 200-kDa antigens within the basement membrane zone.

Benign fibrous histiocytoma (dermatofibroma) may sometimes mimic dermatofibrosarcoma protuberans clinically if it attains a large size. A man

presented with a chronic bleeding enlarging sarcoma-like lesion involving the whole of his left buttock and upper thigh was presented. Clinically its irregular features and large size resembled a malignant tumor but the lesion was a benign dermatofibroma on biopsy. It was in fact the **largest benign fibrous histiocytoma in the world** ever reported. Good communication between dermatologist and dermatopathologist is essential in this case to avoid unnecessary extensive surgery and reconstruction.

Finally, Dr. Calonje presented a woman with saddle nose and a diagnosis of Wegener's granulomatosis for many years. She later developed swollen fingers and red painful nodules in her legs. Skin biopsy was performed to confirm cutaneous vasculitis. The biopsies however showed mixed panniculitis and, with Fite-Wade stain, multiple bacilli. The patient in fact had **erythema nodosum leprosum** (ENL) and **lepromatous leprosy** misdiagnosed as Wegener's granulomatosis. A type II lepra reaction, ENL occurs in up to 70% of patients with lepromatous leprosy. Its pathogenesis appears to be related to immune complex mediated vasculitis.

Learning points:
Good communication between dermatologist and dermatopathologist is essential to avoid pitfalls in diagnosis. Careful history, examination and clinico-pathological correlation are important and mandatory.

Current Concept in Pathophysiology and Treatment of Acne Vulgaris

reported by Dr. T. Y. Ho

Date:	18 April, 2000
Venue:	Sheraton Hotel, Hong Kong
Speaker:	Dr. Ana Beatris Rossi
Organizer:	HKSDV; Scientific Meeting

Pathophysiology of acne vulgaris

There are four essential features in the pathogenesis of acne: ductal abnormal keratinization, sebum production, bacterial colonization and inflammation.

Abnormal keratinization taking place at the infra-infundibulum causes abnormal desquamation of corneocytes and obstruction. Alterations in sebum lipids, such as increase in free fatty acids and decrease in linoleic acid contribute to ductal hyperkeratosis. There is evidence that cytokines are involved in ductal changes. Interleukin-1a, for example, can stimulate hyperkeratosis.

The sebaceous gland is hormonally controlled, especially by androgens. Although high levels of androgens causes acne, the levels of hormones are normal in the majority of patients.

The significance of *Propionebacterium acnes (P. acnes)* in the pathogenesis of acne is demonstrated by the finding that only antimicrobials which specifically suppress *P. acnes* can produce clinical benefit. *P. acnes* stimulates the hydrolysis of triglycerides into free fatty acids, which can lead to irritation. *P. acnes* can also cause liberation of chemotatic factors and release of lysosymal enzymes that result in follicular rupture.

Inflammation is present in acne lesions even at an early stage. A mononuclear infiltrate of T cells can already be detected in microcomedomes. In the early stage of the papular lesion, a type IV inflammatory reaction is present. The antigenic stimulation could be bacterial or products from the pilosebaceous duct. At a later stage, this is followed by a polymorphonuclear infiltration. With the rupture of the pilosebaceous units, there is a non-specific macrophage reaction, with giant cells present.

Treatment options for acne vulgaris

The decision as to whether to use topical, oral or combined therapy for acne vulgaris depends on the acne grading, skin sensitivity, psychological expectations,

previous therapies and the doctor's experience with different drugs.

Oral isotretinoin is the only available oral retinoid for treating acne. It is extremely effective but the incidence of side effects is considerable, with the most severe being teratogenicity. Others range from dryness of skin and mucous membrane to depression, alteration in osteosynthesis and pseudotumour cerebri.

Many oral contraceptives have a favourable effect on acne by suppressing ovarian androgen production and causing a rise in the level of the sex hormone binding globulin (SHBG), thus reducing free androgens. Cyproterone acetate is effective in acne because it reduces androgen production, decreases sebum production and increases the linoleic acid content in sebum.

Oral or topical antibiotics are useful in acne by reducing the numbers and function of *P. acnes*. They also have a direct anti-inflammatory effect by reducing free radicals and chemotaxis of polymorphs. However, antibiotic resistance is an issue that has to be considered nowadays.

Topical retinoids have been used for over 25 years in the treatment of acne vulgaris and can be prescribed in all clinical presentations of acne, due to their comedolytic, anti-comedogenic and anti-inflammatory action. A common adverse effect of topical retinoids is skin irritation, with patients complaining of erythema, scaling and burning sensation. Irritation can often lead to non-compliance. The advantages of adapalene compared with other topical retinoids are the lower rate of irritation, photostability and the anti-inflammatory action. When used with other topical treatment such as benzoyl peroxide and antibiotics, there is no increase in the irritating potential of each product.

Topical combined therapy is the first choice in many cases of mild to moderate inflammatory acne. The regimen usually consists of drugs that act on the keratinization process, such as retinoids, and others with antibacterial or anti-inflammatory effects, such as benzoyl peroxide and antibiotics.

Whatever the choice of initial treatment, maintenance therapy is important. Topical retinoids are the best choice for maintenance therapy because they can prevent new lesions by reducing ductal keratinocyte proliferation and modulating their differentiation.

In treating patients with acne, communication is very important. The patient should be given a feeling of optimism but also a realistic expectation of the progress. With topical retinoids, for example, there is usually little improvement in the first month but by 2 months, there should be 20-40% improvement, and by 4 and 6 months, 40-60% and 80% respectively. Patience and persistence are to be encouraged.

Conclusion

Acne vulgaris is a common, multifactorial disease. The choice of treatment should be tailored basing on the clinical and psychological evaluation of each patient. Communication and rapport with the patient is important to achieve satisfactory improvement.

Learning points:

Topical retinoids is useful in all stages of acne. Patients should be encouraged to be persistent with the treatment, as improvement may not be evident in the first few months.

Terbinafine in Dermatomycoses: Update on Safety and Efficacy

reported by Dr. W. S. Lam

Date:	10 April, 2000
Venue:	Hotel Miramar, Hong Kong
Speaker:	Dr. Carle Paul
Organizer:	HKSDV

Terbinafine is the first orally active allylamine antifungal agent. It specifically inhibits fungal squalene epoxidase which is essential for synthesis of ergosterol, a component of fungal cell membrane. Its action on dermatophyte is fungicidal.

Pharmacokinetics of terbinafine

It is well absorbed from the gastrointestinal tract. It is highly lipophilic and keratophilic. The skin is reached mainly by diffusion from dermal vessels, excretion with sebum, and incorporation into basal keratinocytes. It appears in the nail via nail bed and matrix by diffusion and via matrix by incorporation into the growing onychocytes. The drug appears in the nails at an effective concentration after 7 days and persists in the nails for 3-6 months. The drug concentration is higher than the minimal inhibitory concentrations of most nail pathogens by a factor of 5-50 times after 3 months. This long-term accumulation allows a relatively short period of treatment for fungal nail infections.

Efficacy of terbinafine

It achieves a mycological cure rate of more than 80% in tinea pedis and tinea corporis with a 2-week course of 250 mg/day. Similar cure rate is reached in tinea capitis with a 4-week course of 250 mg/day.

In a double blind, randomised study of continuous terbinafine in treatment of toenail onychomycosis, terbinafine achieved a mycological cure rate of 76% and a complete cure rate of 46% with a 12-week 250 mg/day course after 72 weeks from start.

Regarding cost-effectiveness, the cost of treatment of onychomycosis is far more than the price of the drug. Physician consultations, administrative cost, mycology and laboratory investigations, treatment duration, cure and relapse rates are other factors to be considered.

Safety of oral terbinafine

The safety of oral terbinafine was evaluated in a post-marketing surveillance study of 25,884 patients. The median duration of treatment was 12 weeks. The incidence of adverse events was 10.5%, with the gastrointestinal system (4.9%) and skin (2.3%) involved in the majority. Hepatobiliary events were reported in 0.2% of all patients. Terbinafine was considered to be a possible or probable cause of 11 (0.04%) serious adverse events. Two persons (0.008%) presented with symptomatic hepatobiliary dysfunction possibly or probably related to terbinafine.

In another cohort study on the risk of acute liver injury among 69,830 users of anti-fungal drugs, the incidence rate were 134.1 per 100,000 person-months for ketoconazole, and 2.5 for terbinafine. The background rate of acute liver injury during the non-use of oral antifungal drugs was 0.6 per 100,000 person-months.

According to the speaker, the incidence of symptomatic hepatic dysfunction during treatment with terbinafine was 7.4-7.7 per 100,000 patients treated while the incidence of life-threatening hepatic dysfunction or death was 1 per 2,000,000 patients treated. Thus symptomatic liver dysfunction was very rare and peak incidence was between 3-6 weeks of therapy. The pattern of liver injury was cholestatic in 64%, hepatocellular in 12% and mixed in 24%. It was reversible with discontinuation of the drug in more than 99%.

Prevention of hepatic dysfunction with terbinafine

Firstly, caution should be taken in patients with risk factors for liver impairment like elderly, concomitant use of hepatotoxic drug and chronic/active liver disease. Secondly, to check liver function at baseline and four or six weeks. If there is a history of

chronic or active liver disease, its use is not recommended in general and a risk/benefit assessment of the use of the drug should be made before a decision is made. If there are signs and/or symptoms of liver dysfunction, it is necessary to discontinue terbinafine and check liver function.

Drug interaction

Terbinafine is metabolized by four major pathways: N-demethylation, deamination, alkyl side chain oxidation and dihydrodiol formation. At least seven cytochrome P-450 (CYP) enzymes (isoforms) are involved in its metabolism. It has little or no effect on the metabolism of many cytochrome P-450 substrates. However it is a competitive inhibitor of the CYP2D6 isoform and may reduce elimination of drugs metabolized by CYP2D6. Drugs predominantly metabolized by CYP2D6 include tricyclic antidepressant, b-blocker, selective serotonin re-uptake inhibitor and monoamine-oxidase inhibitor. It is necessary to closely monitor for side effects, and if necessary, to reduce the dose of terbinafine when a CYP2D6 substrate is co-administered.

Conclusion

The author concluded that terbinafine had high-to-superior sustained efficacy, good tolerability, single once daily dosage and superior cost-effectiveness under appropriate medical supervision.

Learning points:

The use of terbinafine in patients with chronic or active liver disease is not in general recommended and a risk/benefit assessment needs to be made before a decision is made. The co-administration of terbinafine and other CYP2D6 substrates may cause drug interaction, necessitating close monitoring for side effects and dose reduction.

Botulinum Toxin Type A Injection in Facial Enhancement

reported by Dr. W. S. Lam

Date:	29 April, 2000
Venue:	Regent Hotel, Hong Kong
Speaker:	Dr. L. S. Baumann
Organizer:	HKSDV and Hong Kong Society of Plastic and Reconstructive Surgeons

Botulinum toxin type A (BTX-A) injection is the fastest growing cosmetic procedure in the US in 1999 and ranks as the second most common aesthetic procedure in the US.

Botulinum toxin type A

BTX-A is one of seven distinct botulinum toxin serotypes and is the only one currently licensed for specific clinical indications. It is secreted by the bacterium *Clostridium botulinum*. Two BTX-A products, Botox and Dysport, are commercially available but they are not interchangeable.

BTX-A is a 150 kDa protein complex made up of a 100 kDa heavy chain linked by a disulphide bond to a 50 kDa light chain. The heavy chain binds to cholinergic nerve terminal and transports the toxin inside. Once inside cell, the light chain dissociates and cleaves a target protein, blocking release of acetylcholine transmitter. This produces focal muscle relaxation and inhibition of sweating. Thus the former has been used to lessen facial lines/wrinkles and the latter to treat hyperhidrosis.

Handling and administration of Botox

Each glass vial contains 100 units of Botox as a vacuum-dried product. It can be stored at or below -5°C. It can be reconstituted with preservative-free normal saline. During preparation, draw up diluent e.g. 2.5 ml normal saline and gently inject into vial. Gently rotate vial and do not shake. Record date and time of reconstitution. The resulting dose is 4.0 unit per 0.1 ml. Do not freeze Botox once reconstituted as ice crystals may form, damaging the toxin and reducing potency.

Store it in the refrigerator. Other factors affecting potency are listed in Table 1. Regarding storage time of diluted toxin, current practice is to store up to one week with dosage increased by 50% after one week to compensate for loss of potency.

Table 1. Factors affecting potency of Botox

1.	Use of benzyl alcohol as a preservative
2.	Alcohol on the skin or bottle cap
3.	Bubbles caused by foaming
4.	Agitation of the bottle or syringe
5.	Storage time of diluted toxin

Use of Botox in facial enhancement

The general principle is to inject with 30 gauge needles for minimizing patients' discomfort. Wipe the area to be injected with alcohol and allow to air-dry first. Have the patient contracted the muscles, mark the injection sites and inject with patient's muscle relaxed for comfort. BTX-A is most useful for the cosmetic enhancement of the upper face. Basic indications include glabellar frown lines, crow's feet and forehead lines.

For glabellar frown lines, the sites of injection and dose are determined by muscle mass. For the horizontal, male-type brow, because of greater muscle mass, more toxin and more sites are necessary. For the arched, female-type brow, less toxin is required. 20-48 units of Botox are used. Chill the area to be injected or use topical anesthetic (e.g. EMLA) if necessary. Injection sites should usually be above the supraorbital rim and medial to the mid-pupillary line. Massage procerus injection inferiorly to diffuse toxin into depressor supercilii muscle. After injection, advise patients to frown as much as possible during the next 2-3 hours. Follow-up patients in 2-4 weeks' time. Photograph patient and assess results. The average duration of effect after the first injection is about 18 weeks. Re-injection schedule is patient-dependent, usually at 3-4 months intervals for first year. Less frequent re-injection may be necessary after repeated treatments.

For crow's feet, the patient is asked to smile maximally. Note the upper and lower borders of the crow's feet and mark them. Palpate the orbital rim - approximately 1.5 cm from the lateral canthus. Inject 0.1 ml (4 units) at this site and 1 cm above and below this site, totally 12-18 units per side.

For horizontal forehead lines, careful evaluation is required. It is necessary to differentiate individuals who overuse the frontalis expressively from those compensating for a pre-existing brow ptosis. Approach should be conservative and 20-40 units Botox in 4-10 divided doses are usually given. Inject lateral to mid-pupillary line and stay 2 finger widths above the rim of the supraorbital rim.

More advanced cosmetic applications include treatment of upper lip lines, nasal scrunch, nasal flare, mental crease and facial asymmetry, etc. Combination approaches may be used, e.g. Botox plus topical agents to chemically peeled selected areas, fillers or laser resurfacing. Electromyography can be used as an adjunct to localize small muscles and as a teaching tool. However it will lengthen the procedure, necessitate the use of a 27-gauge needle and increase the expense.

Side effects of botulinum toxin type A injection

Ptosis of brow or lid may occur after BTX-A injections and usually resolves in 1-10 weeks. Apraclonidine eyedrops can be used to temporarily reverse the ptosis. Local temporary swelling or bruising may also occur. Depending on the amount of neurotoxin protein contained in the preparation, production of neutralizing antibodies may occur.

Conclusion

Botulinum toxin type A injection is an useful technique in upper facial enhancement with occasional temporary side effects.

Learning points:

Botulinum toxin type A injection is a relatively simple way to treat upper facial lines though regular injection every 3 to 4 months is necessary to maintain the effect.