

Annual Scientific Meeting of the Hong Kong Society of Dermatology and Venereology 2007

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Date: 24 June, 2007
Venue: Sheraton Hotel, Hong Kong
Organiser: Hong Kong Society of Dermatology and Venereology

HPV vaccine – the dos and don't

Speaker: Professor Ngan Yuen-sheung
Professor, Department of Obstetrics and Gynaecology,
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Cervical cancer ranks second and fourth as the commonest female cancer worldwide and in Hong Kong respectively. Human papilloma virus (HPV) is a small DNA virus and about 50% of sexually active adults will have HPV infection in their lifetime. The oncogenic types of HPV are an important but not the sole cause of cervical cancer. Other risk factors include young age of sex debut, smoking, the use of oral contraceptive pills, high parity and presence of sexually transmitted diseases.

In HPV infection, less than 1% of cases develop cervical intraepithelial neoplasia (CIN)-3 and 0.1-0.3% of cases develop cancer. HPV type 16 and 18 cause about 70% of cervical cancer and type 6 and 11 cause about 90% of genital wart. The prophylactic vaccine for HPV infection targets at HPV type 6, 11, 16, 18. The vaccine is composed of recombinant viral L1 capsid protein, which induces IgG antibody response

and prevents the binding of virus to the cell surface. In a phase III trial, the efficacy for preventing high grade CIN caused by HPV 16 and 18 was 98% for according to protocol vaccine recipients. However since this is a prophylactic vaccine, it is therefore best recommended for females before sex debut. The vaccine is currently registered for use in female age between 9 and 26 years. It is also important that cervical cytology screening should be continued to achieve the best outcome to prevent cervical cancer.

The vaccine should not be regarded as substitution of cervical screening. The vaccine should not be given to those with a history of allergy to any of the vaccine components and pregnant women. Pre-vaccination serology or HPV DNA test are not required as these tests are not reliable to detect prior HPV infection. Checking of contraindication and understanding the limit of HPV vaccine by both the physician and patient is necessary before vaccination.

Learning points:

The quadrivalent HPV vaccine targets at HPV type 6, 11, 16, 18. It is best recommended currently for female before sex debut. The vaccine is not a substitute for cervical screening, which is still important as not all HPV subtypes are covered by the vaccine.

Interpretation of immunological tests

Speaker: Dr. Chan Yuk-tat, Eric

Consultant, Division of Clinical Immunology, Department of Pathology and Clinical Biochemistry, Queen Mary Hospital, Hong Kong

A number of skin diseases are autoimmune in nature and are characterised by the presence of skin blisters while many other systemic autoimmune diseases have cutaneous manifestations. Autoantibody tests are important in the diagnosis and management of patients with autoimmune diseases. One autoantibody often can be measured by several techniques with different interpretation of results.

Anti-nuclear antibodies (ANA) are mainly used for screening of rheumatic diseases. This is typically done by indirect immunofluorescence test on HEp-2, a human epithelial cell line, as an antigen source. ELISA is more commonly used for measuring ANA. ANA is sensitive but not specific for systemic lupus erythematosus (SLE). Titre of 1/40 is found in 20% of normal population. It correlates roughly with the disease activity. A positive result of ANA requires further identification of specificities by checking antibodies against, for example, double strand DNA (ds DNA) and extractable nuclear antigen (ENA). Anti-ds DNA antibody is more specific for the diagnosis of SLE and its level can be used to monitor disease activity. Anti-ENA antibody commonly tested includes anti-Sm (specific for SLE), anti-nRNP (mixed connective disease), anti-Ro and anti-La (cutaneous lupus and congenital lupus), anti-Jo-1 (polymyositis/ dermatomyositis associated with interstitial lung disease) and anti-Scl-70 (progressive systemic sclerosis).

Vasculitis is a clinicopathologic process with inflammation and necrosis of blood vessels. Some of the diseases in this group are characterised by the presence of anti-neutrophil cytoplasmic antibody (ANCA). There are two main patterns of ANCA, namely peripheral (p-) ANCA and cytoplasmic (c-) ANCA. Antibody against

myeloperoxidase (anti-MPO) is usually detected in sera with p-ANCA and is associated with microscopic polyarteritis, Churg-Strauss syndrome and pauci-immune glomerulonephritis. Antibody binding proteinase III (anti-PR3) is usually present in sera with c-ANCA and is characteristic of Wegener's granulomatosis. The level of anti-MPO and anti-PR3 is used to monitor the disease activity.

Antibodies against desmosomal antigens of epidermal cells are responsible for pemphigus vulgaris (PV) and pemphigus foliaceus (PF). The level correlates with the disease activity. Antibodies binding the lamina lucida of the basement membrane at the dermo-epidermal junction, namely bullous pemphigoid antigen (BPAg) 1 and BPAg2 are identified in bullous pemphigoid. BPAg2 is responsible for the induction of blisters.

Learning points:

A number of skin diseases are autoimmune in nature while many other systemic autoimmune diseases have cutaneous manifestations. Immunological tests are important in the diagnosis and management of patients with these diseases.

Skin patch test – its interpretation and application

Speaker: Dr. Lee Tze-yuen

Honorary Clinical Associate Professor, Faculty of Medicine, University of Hong Kong, Hong Kong

Contact dermatitis is an inflammatory condition of the skin caused by an external agent. Types of contact dermatitis include irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), phototoxic contact dermatitis and photoallergic contact dermatitis. A detailed history is most important for diagnosis, but sometimes clinical judgement can be misleading. Skin patch testing is an important diagnostic tool in contact dermatitis.

The most commonly used test kits for patch testing at present include the Finn Chambers on Scanpor tape, I.Q. Chambers and the TRUE (thin-layer rapid use epicutaneous) test. Commercially prepared allergens are supplied in syringes and are grouped to form different series catered for different situations, e.g. perfume series, dental series, photographic chemical series, etc. Photopatch test is used to evaluate contact photoallergy to common photoallergens.

False positives can occur as a result of contamination, high concentrations of allergens, reaction to patch testing materials, artefacts and the excited skin syndrome. The excited skin syndrome occurs where the skin is hyperirritable due to a strong test reaction, rendering negative tests as being weakly positive.

False negative results can occur with low concentrations or small amounts of allergens, inappropriate occlusion, reading results too early, suppression by steroid or failure to observe a delayed reaction after 48 hours (e.g. in immunosuppressed individuals).

Patch testing is generally a safe procedure but adverse reactions may sometimes occur. They include active sensitisation, irritant reactions to tape, pigmentation changes, secondary infection, scarring, flare up of existing dermatosis and anaphylactic reactions. Patients may also find it troublesome and might not have time to return for follow-up assessment.

In a study on the acceptability and usefulness of patch testing in Hong Kong, the acceptance rate for 3 groups of patients (contact dermatitis, endogenous eczema and unclassified eczema) were found to be 85.7%, 69.2% and 83.3% respectively with an overall acceptance rate of 81%. After comparing the pre- and post-patch test diagnoses, it was found that in 21.7%, 18.7% and 28.0% of the respective groups of patients (overall 22.7%), the final diagnosis had to be changed or modified. This shows that skin patch test is indeed

a very useful test in the aetiological diagnosis of dermatitis.

In another study, patch testing in 490 patients in Hong Kong during a period of 12 months showed that the top 4 allergens in the European standard battery of allergens that gave positive reactions include fragrance mix (19.5%), nickel (16.4%), cobalt (11.3%), and balsam of Peru (8.6%). Among the materials brought by patients, herbal medicine and western medicine were the most common ones that gave positive reaction. In comparison, nickel was the most common allergen in Beijing, Taipei and Singapore. Fragrance mix was the second commonest allergen in Taipei and Singapore whilst it ranked fifth in Beijing, suggesting difference in the use of cosmetics.

Learning Points:

Skin patch testing is an important diagnostic tool in contact dermatitis in conjunction with a detailed clinical history. It is important to be aware of false-positive and false-negative patch test results. In Hong Kong the top four allergens are fragrance mix, nickel, cobalt and balsam of Peru.

Pemphigus with a simple logic behind complex phenotype

Speaker: Professor Masayuki Amagai
Professor and Chair, Department of Dermatology,
Keio University School of Medicine, Japan

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are autoimmune blistering diseases characterised by intraepidermal blisters formation. PV typically presents with painful erosions and flaccid blisters on skin and mucous membranes, whereas PF has scaly crusted cutaneous erosions with no mucosal involvement. Histologically, the intraepidermal blisters are subcorneal in PF and suprabasilar

in PV, due to an ongoing process of epidermal acantholysis leading to blisters formation. In early 90s, the isolation of cDNA using molecular biology revealed PF and PV antigens were desmoglein 1 (Dsg 1) and desmoglein 3 (Dsg 3) respectively. They are cadherin-type cell-cell adhesion molecules expressed in skin and mucous membranes. In late 90s, enzyme-linked immunosorbent assay (ELISA) using recombinant extracellular domains of Dsg 1 and Dsg 3 expressed by baculovirus system was developed as a specific and sensitive detection tool for pemphigus autoantibodies. A serum from PF is positive against Dsg 1 but negative against Dsg 3. If the serum is negative against Dsg 1 but positive against Dsg 3, it suggests a diagnosis of mucosal dominant type of PV. If the serum is positive against both Dsg 1 and Dsg 3, then it indicates the mucocutaneous type of PV. The desmoglein compensation theory can now explain the clinical and microscopic localisation of PF and PV blisters at a molecular level. The theory states that Dsg 1 and Dsg 3 compensate for each other to maintain epidermal integrity. For example, when the serum contains only anti-Dsg 1 IgG which interferes with the function of Dsg 1, then the serum causes blisters only in the superficial epidermis since this is the only area in which Dsg 1 is present without coexpression of Dsg 3. In the unaffected deep epidermis, the presence of Dsg 3 compensates for the loss of function of Dsg 1. Although anti-Dsg 1 IgG also binds to the mucosa, no blisters are formed due to the coexpression of Dsg 3 in the mucosal membrane. Thus, serum containing only anti-Dsg 1 IgG causes superficial blisters in the skin without mucosal involvement as in PF. More recently, autoantigen deficient mice which do not acquire tolerance against the defected autoantigen provides an active disease model for pemphigus. Adoptive transfer of Dsg 3-/- lymphocytes to mice expressing Dsg 3 induces stable anti-Dsg 3 IgG production with development of the pemphigus phenotype. This mouse model provides a valuable tool to study

the molecular and cellular mechanisms of harmful IgG autoantibody production in pemphigus.

Learning points:

The desmoglein compensation theory has enabled the clinical and histopathological features of PF and PV to be logically explained. Further molecular advances will allow the pathophysiological mechanisms of pemphigus to be more thoroughly studied.

Genital HPV infection – clinical significance and management

Speaker: Dr. Lo Kuen-kong

Consultant Dermatologist in-charge, Social Hygiene Service, PHSB, CHP, Department of Health, Hong Kong

Genital Human Papillomavirus (HPV) infection is one of the most common sexually transmitted diseases (STD) in Hong Kong. There are different clinical manifestations of the infection, genital warts being the commonest and cervical cancer being the most serious. Clinically, genital warts are characterised by growth in the genitalia. There are four types according to the morphological presentation, which include the cauliflower type (typical condylomata acuminata), papular type, keratotic type and flat-topped papules or macular type.

Genital warts should be differentiated from a number of anatomical variants like skin tags, naevi, vestibular papillomatosis in female and pearly penile papules in male. Other differential diagnoses include genital warts like molluscum contagiosum, condylomata lata, squamous cell carcinoma and seborrhoeic keratosis.

There are more than 100 genotypes and many more subtypes identified for HPV. Over 40 types infect mucosal surfaces or cause anogenital warts.

Anogenital warts are therefore not only caused by a single or a few HPV genotypes.

Many other types of HPV can cause different genital conditions that are not traditionally classified as STD. Cervical carcinoma in situ and vulval intraepithelial neoplasia are the two main conditions that are important as they can both progress to malignancy. HPV can be divided into high risk and low risk types according to association with cancer. High risk types include HPV 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 68 and 82. Low risk types include HPV 6 and 11. The commonest types that can be identified in cervix of the female attendees of the public STD clinics in Hong Kong are HPV 6, 11, 16 and 58.

Genital HPV infection is ubiquitous and is generally transient. The lifetime acquisition rate ranges from 60% to 80%. The prevalence of genital HPV infection in sexually active population ranges from 20% to 46%. Only 1% of the genital HPV infections results in overt genital wart. There is no curative treatment for genital HPV infection but fortunately most of them can remit by itself and the infection is transient. Three therapeutic goals are recommended for the clinical management of anogenital wart: a) the results of therapy must be no worse than the disease itself, b) it aims at induction of warts free periods but not for eradication of HPV infection, and c) monitor for cervical cancer for female.

Options of treatment of genital warts include topical application of podophyllin, podophyllotoxin, trichloroacetic acid, 5-fluorouracil, cryotherapy, electrosurgery, excision, carbon dioxide laser vaporisation, imiquimod and intralesional interferon. They all have their advantages and disadvantages, and the choice depends on many factors. The best strategy of prevention and risk reduction of anogenital warts nowadays is still the adoption of safer sex measures.

Learning points:

An understanding of the clinical differential diagnoses, HPV genotypes and treatment of anogenital wart is important for the better management of this common sexually transmitted infection.

Cutaneous manifestations of rheumatological diseases

Speaker: Professor Stephen Lee

Clinical Associate Professor, Department of Medicine, University of Sydney, Australia

People with rheumatological diseases (RD) can be found worldwide and there is often no definitive cure. Most of these people do not die of the disease. However, they live with multiple health problems, such as organ system failure, immobility and gross disfigurement. The latter is uncommonly dermatologically related.

One of the best illustrative examples of RD with cutaneous manifestation is systemic lupus erythematosus. It highlights the potential of RD as a cause of chronic and recurring damage to multiple organs including the integument, resulting in significant morbidity and fatal outcomes. Cutaneous manifestations of the other RD may be less dramatic, transient and self-limiting and are therefore not easily be detect.

In management of RD, skin signs aid early diagnosis and timely commencement of appropriate treatment. Most of the more prevalent RD in active phase can be diagnosed on clinical grounds alone. However, at times, investigations are necessary and skin biopsy with histological examination can be useful.

Learning points:

Cutaneous manifestations of rheumatological diseases have to be recognised as they aid early diagnosis and timely commencement of appropriate treatment.