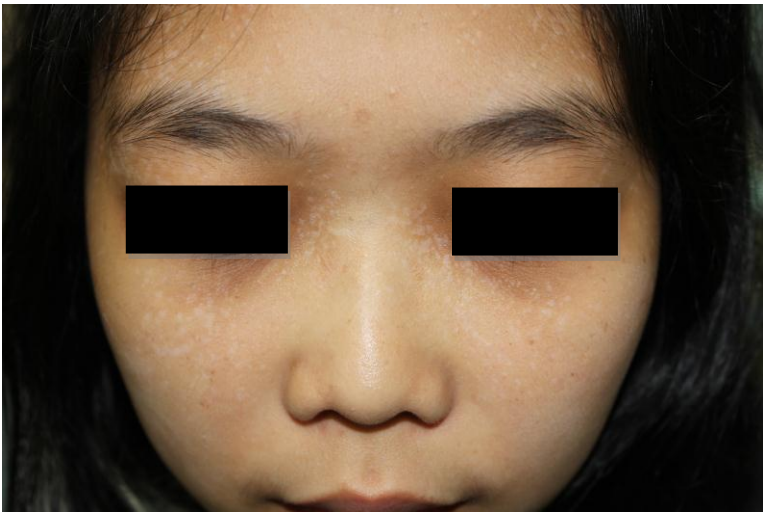
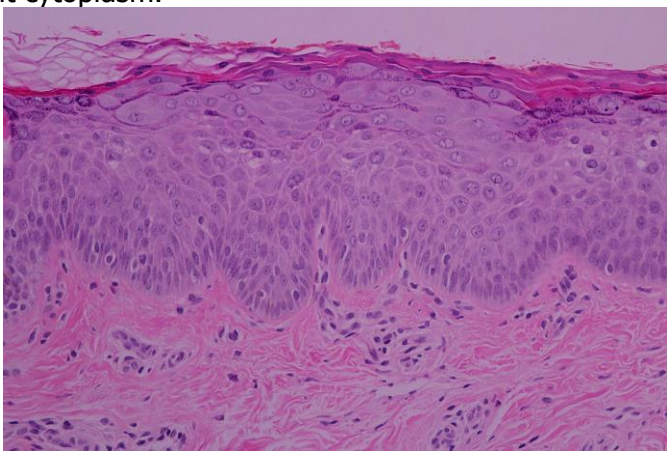
Case 12
An 18-year-old Thai woman from Bangkok.
Chief complaint: Multiple hypopigmented macules at face for 6 months.



Present illness: The patient noticed multiple asymptomatic hypopigmented macules on her face for 6 months. It was slowly progressed to entire her face.
Past history:She was diagnosed with Evan's syndrome since March 2012 (presented with thrombocytopenia and autoimmune hemolytic anemia). She had initially undergone with prednisolone 60 mg/day and then the dose was tapered. Along with follow up period, she developed proteinuria and blood sample for ANA was positive, titer > 1:1280 ,fine speckle pattern. Therefore, her diagnosis changed to systemic lupus erythematosus. she started treatment with chloroquine 250 mg/day, prednisolone 15 mg/day and azathioprine 50 mg/day
Family history : She is the only child. Her parents are not consanguineous. No family member of the patient had a similar disease.

Physical examination
HEENT: not pale, no jaundice, no malar rash, no discoid rash, no oral ulcer
Lymph node: no palpable axillary and supraclavicular node
Abdomen: no hepatosplenomegaly
Ext : pitting edema 1+
Skin examination
Multiple discrete hypopigmented macules distribute symmetrically entire face
Labs: CBC : WBC 4,680 /cumm (N77%, L14%, M6%,E2%), Hb 10.9g/dl, Hct 32.6%, Plt 60,000 /cumm
Direct Coombs' test positive 3+, Indirect Coombs' test positive 3+
Proteinuria 3.2 gm/day
ANA was positive, titer > 1:1280 , fine speckle pattern
Anti-dsDNA negative, Anti-sm negative, Anti-Ro positive 1+, Anti-La negative
Anti-HIV negative
Histopathology (S12-24366, Rt side forehead)
There is hyperkeratosis, hypergranulosis and epidermal hyperplasia with some large keratinocytes with vesicular nuclei and basophilic abundant cytoplasm.



Tissue Biopsy for HPV sequencing: Cannot investigate HPV genotype due to viral load less than 2000 copies/ml
Genetic testing : mutation on EVER1 gene located on exon 5 and exon 6

Diagnosis: Epidermodysplasia verruciformis
Systemic lupus erythematosus
Treatment: 5% imiquimod apply 3 times per week
Photoprotection and broad spectrum sunscreen

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Discussion

Epidermodysplasia verruciformis(EV) is a rare genetic disorder that is characterized by a susceptibility to cutaneous infection with specific human papillomavirus (HPV) types, called EV-HPV type. The disease was first described by Lewandoski and Lutz in 1922.[1] EV results from a genetically determined defect in cutaneous immunity that leaves afflicted individuals susceptible to persistent HPV infection.[1] The mode of inherited was thought to be autosomal recessive, by the way an X-linked recessive and autosomal dominant has also been reported.[2-3] Although the familial form of EV has been reported to be more common, few cases had sporadic appearance of the disease.[4]

Mutations in EVER1 and EVER2 genes on chromosome 17q25 [epidermodysplasia verruciformis susceptibility locus 1 (EV1)] that encode integral membrane proteins in the endoplasmic reticulum are responsible for the condition.[5] However, an international collaborative study revealed that only 75% of EV patients carry homozygous nonsense mutations in either EVER1 or EVER2[6], and other studies have reported patients EV patients that did not carry mutations in the EVER genes.[3, 7-8]

A second susceptibility locus on chromosome 2 [epidermodysplasia verruciformis susceptibility locus 2 (EV2)] has also been implicated in the cause of epidermodysplasia verruciformis, providing evidence for nonallelic heterogeneity in the disease.[9]

EVER1 and EVER2 belong to the TMC (transmembrane channel-like) gene family and are therefore also termed TMC6 and TMC8, respectively. Although the proteins encoded by the EVER genes have been shown to localize in the endoplasmic reticulum with features of integral membrane proteins, the exact function in development of persistent HPV infections has not yet been revealed.[10] It has been hypothesized that these proteins act as restriction factors for epidermodysplasia verruciformisspecific HPVs in keratinocytes, and that epidermodysplasia verruciformis represents a primary deficiency of intrinsic immunity against certain papillomaviruses.[6]

EV-HPV type occasional referred to as the beta papillomaviruses, the most frequently implicated types are HPV-5 and HPV8 which have potential associated malignant transformation. Furthermore other EV-HPV type that have been reported include HPV-9,-12,-14,-15, -17,-19,-25,-36,-38, -47,-50.in our patient, we can't identified HPV genotype genotype due to a low viral load.

Clinical presentation of classic EV mostly are asymptomatic and first appears during childhood with various cutaneous lesions such as pityriasis versicolor like, wart-like papules, flat, slightly scaly, red-brown macules and pinkished-red plane papules on the face, neck and body. [11] In 30–70% of the cases cutaneous skin cancer develops and malignant transformation of lesions is especially seen after the age of 30 years. While most of the skin cancers occur on sun-exposed skin, it can also be localized to any part of the body. Because of the development of cutaneous carcinomas particularly on sun-exposed skin, it has been claimed

that UV-light acts as a cofactor. The onset age of skin cancer is in the third and fourth decades.[4]

Histopathologically, the most characteristic EV findings occur within the epidermis. The classic histologic presentation resembles that of verruca plana, with mild to moderate hyperkeratosis, acanthosis with bridging of rete ridges, and enlarged, vacuolated keratinocytes (koilocytosis) that have perinuclear halos and blue-gray pallor on hematoxylin-eosin staining.[12]

EV lesions have occasionally been described in immunosuppressed populations including patients with HIV, renal transplantation, Hodgkin's disease, and SLE. [13-14] EV occurs presumably as a result of immunodeficiency or prolonged treatment with corticosteroids. In our patient, she received the treatment with corticosteroids and immunosuppressive drug during these lesion developed. However the result of genetic testing in this patient was positive for EVER1 mutation. Therefore in this patient, the diagnosis was inherited EV. Nevertheless, treatment related immunosuppressive state in combination with genetic mutation may precipitated the symptom in this patient.

An effective therapy for EV has not yet become available. The management of warts in EV is dependent on the age of the patient, the extent of the lesions, the immunological status, and the patient's desire for therapy. EV is associated with lifelong eruption of disseminated verrucae-like lesions and malignant transformation during the fourth to fifth decades. For localized malignancies surgery is still the best option, but for the persistent widespread nonmalignant lesions surgical measures are impractical.

Local therapy such as cryotherapy, curettage, surgical excision or CO2 laser is limited to EV patients with extensive, resistant, highly recurrent lesions. Topical retinoids have shown efficacy in only one case.[15] Imiquimod has been used, with varying success.[16-18] Our patient was instructed to apply topical imiquimod 3 days weekly for 1 months and then daily for5 months on the face,

which was well tolerated and resulted in significant improvement.

For systemic therapy, successful treatment with etretinate [19], acitretin (0.5-1 mg/kg/day) or combination with recombinant interferon[20], oral isotretinoin (0.3-0.8 mg/kg/day) have been reported.[21] And patients should be educated on sun protection given their increased risk of development of NMSC.

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