Diffuse skin-colored papules in a child

Bret Kenny, MEng¹; Irina Oroz, MD²; Allison Osmond, MD, MSc³

¹Faculty of Medicine, Memorial University, St. John’s, NL, Canada; ²Dermatology, University of Saskatchewan, Saskatoon, Canada; ³Department of Pathology and Laboratory Medicine, Saskatchewan Health Authority, Saskatoon, Canada.

Word Count: 1028
Reference Count: 4
Figure Count: 3

Declaration of Conflicting Interests: The authors have no conflicts of interest to declare related to this work. Written informed consent for the case to be published was obtained from the patient, including accompanying images and medical history.

Funding: None

Corresponding Author:
Bret Kenny
163 Empire Avenue
St. John’s, NL
A1C 3G6
Canada
Mobile: +1 (709) 725-2764
Email: bret.kenny@mun.ca

Keywords: Epidermodysplasia Verruciformis, Human papillomavirus (HPV)
A 9-year-old female presented to an outpatient dermatology clinic with a 3-year history of asymptomatic skin lesions and an unremarkable personal, family, and medication history. Skin examination revealed erythematous to skin-colored, flat-topped, polygonal, papules ranging in size from <1mm to 4mm. The lesions gradually increased in size and number since initial onset; 100s of well-defined lesions with scant scale were generalized in a random, generally symmetrical pattern, with some coalescence affecting the lateral neck, chest, back, upper and lower eyelid areas, as well as the medial, ventral aspect of the wrist and dorsal hands. Background skin was normal.

Labs including HIV screening, serum protein electrophoresis (SPE), and complete blood count (CBC) were unremarkable.

Question 1: What is the most likely diagnosis?

A. Disseminated Verruca Plana
B. Lichen Planus
C. Basaloid Follicular Hamartomas
D. Epidermodysplasia Verruciformis
E. WHIM Syndrome

Answers:

A. Disseminated Verruca Plana – Incorrect.
The clinical presentation is similar to disseminated verruca plana which is the top clinical differential diagnosis for this presentation. Similar to our patient, disseminated verruca plana can present in children particularly if there is a co-existent familial incidence and, in this setting, verruca plana includes multiple lesions, however lesions are usually papillomatous, may appear in a linear configuration (due to autoinoculation) and are typically located on the face, dorsal hands, extremities and trunk. Histologic sections of verruca plana will characteristically show hyperkeratosis, absent to vague papillomatous, hypergranulosis, acanthosis and koliocytic appearing cells.

B. Lichen Planus – Incorrect.
The lesion morphology shares similar features with lichen planus. However, the lesions in our case were non-pruritic, a prominent feature of lichen planus. Histologic findings are also not consistent with lichen planus which will show band-like lymphocytic infiltrate at the dermoepidermal junction with degeneration of the basal layer, irregular epidermal hyperplasia with characteristic saw-tooth pattern and wedge shape hypergranulosis.
C. Basaloid Follicular Hamartomas – Incorrect.
The lesion morphology is comparable to basaloid follicular hamartomas; however, our patient did not have lesions over the central face, open comedones, Blaschkoid distributed lesions, hyperpigmented lesions or neurological deficits, features commonly seen in basaloid follicular hamartoma syndrome presentation. Histologic findings are also not consistent with basaloid follicular hamartomas, which will show proliferations of bland basaloid and squamoid cells, arranged in cords and strands, attached to the epidermis with background stromal induction.

D. Epidermodysplasia Verruciformis – Correct.
Epidermodysplasia verruciformis (EV) is a rare genodermatosis characterized by a susceptibility to a group of human papillomaviruses (β-HPV), leading to the development of diffuse and polymorphic cutaneous lesions in the form of papules, plaques, ‘flat wart’ like lesions or pityriasis versicolor like lesions. Onset of the disease is most common within the first decade of life and predominantly affects individuals with abnormal cell-mediated immunity associated with either a primary immune defect or acquired immunosuppression. A punch biopsy of 1 of the clinical lesions confirmed the diagnosis and showed characteristic findings including epidermal acanthosis with expansion of the epidermis by cells with abundant bluish-gray cytoplasm (distinctly characteristic of EV) as well as cleared-out nuclei, perinuclear halos and variably prominent keratohyalin granules.

E. WHIM Syndrome – Incorrect.
While this patient presented with diffuse flat wart like lesions, other lab work including HIV screening, serum protein electrophoresis (SPE), and complete blood count (CBC) were unremarkable, and the patient also lacked a history of infections.

Question 2: What group of viruses are implicated in this skin disease?
A. Human papillomavirus – Correct.
Beta human papillomaviruses (β-HPV) are a group of DNA viruses implicated in the production of various warts on the skin. Specifically, there have been more than 20 different strains of HPV implicated in EV. Some strains of HPV, namely HPV-5, -8, and -14, are associated with higher oncogenic potential of nonmelanoma skin cancer in EV patients. Skin lesions are thought to develop as a result of the cumulative cocarcinogenic effects of genetics, HPV, and UV radiation. Malignancy is usually observed approximately 20-30 years after the formation of benign lesions. The patient in this case was investigated for low-risk (6, 11, 40, 43, 44, 54, 69, 70, 71, E6/E7) and high-risk (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 83, E6/E7) HPV strains using an in-situ hybridization technique. The results of these investigations were negative, and the patient was most likely infected with an alternative HPV strain that has been associated with EV.

B. Coxsackievirus – Incorrect.
Coxsackieviruses are associated with hand, foot, and mouth disease (HFMD). Typical cutaneous lesions include red vesicular macules, papules, and blisters on the dorsal and palmar surfaces of the hands, and ulcerative oral lesions.
C. Poxviridae – Incorrect.
Poxviridae are associated with molluscum contagiosum (i.e. molluscum contagiosum virus). Typical cutaneous lesions include clusters of indurated, red, umbilicated papules that present in moist areas such as the intertriginous regions\(^\text{10}\).

D. Herpes viruses – Incorrect.
Herpes viruses are implicated in several diseases of the skin including herpes zoster (shingles), and herpes simplex for example\(^\text{11}\). Herpes zoster presents with typical vesicular cutaneous lesions confined to dermatomal distribution. Non-genital herpes simplex typically presents with grouped vesicular and eroded cutaneous lesions around the mouth and face, as well as the anogenital region.

E. Polyomaviridae – Incorrect.
Polyomaviridae have been associated with diseases of the skin including Merkel cell carcinomas, trichodysplasia spinulosa\(^\text{1,2}\). Merkel cell carcinoma typically presents with a rapidly enlarging, red, solitary nodule typically on the head and neck. Trichodysplasia spinulosa presents with skin-colored follicular papules with a central keratin spine, typically on the nose and forehead.

Question 3: What is the most common genetic mutation in this skin disease?

Answers:

A. EVER1 and EVER2
B. RHOH
C. MST-1
D. CORO1A
E. IL-7

A. EVER1 and EVER2 – Correct.
The most common genetic etiologies of EV include mutations of the EVER1 and EVER2 genes; approximately 11% of these cases are associated with consanguinity, and 10% from multiplex families\(^\text{1,2}\). EVER1 and EVER2 genes belong to TMC family of proteins (TMC6 and TMC8 account for 75% of cases) involved in zinc homeostasis and downstream signalling cascades important to the immune system\(^\text{1}\). Most EV cases have been reported to have impaired cell-mediated immunity\(^\text{1}\). Given the clinical data available, the patient in this case is presumed to have a sporadic form of EV\(^\text{5}\).

B – E. RHOH, MST-1, CORO1A, IL-7 – Incorrect.
Mutations in RHOH, MST-1, CORO1A, and IL-7 have been reported as case reports in the literature to be associated with EV patients, however these mutations are not the most common\(^\text{1,2}\). RHOH encodes an atypical, hematopoietic cell-specific Rho GTPase. CORO1A encodes coronin-1A, a member of a conserved family of actin-binding proteins. MST-1 is a hepatocyte growth factor-like protein. IL-7 is a hematopoietic growth factor that is involved in differentiation and maturation of all cells in the lymphoid lineage. Patients with these mutations present with a phenotype of disseminated flat wart lesions positive for β-HPV\(^\text{1,2}\).
References:
