CASE REPORT

Disseminated Molluscum Contagiosum in Immunosuppressed Patient: A case report

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ABSTRACT

Molluscum contagiosum is a most frequent self-limiting benign viral skin disease(pox virus). It is usually requires local treatment, only for cosmetic reasons. In the case of typical lesions,The diagnosis is straightforward. Atypical presentations occur commonly in immunocompromised patients and require differentiation from basal cell carcinoma, keratoacanthoma, Darrier's disease and cutaneous cryptococcosis. Individual lesions are often larger than typical (3-5 mm) and may reach as much as 15 mm. The lesions may be numerous and they may coalesce into larger agglomerations and nodules.[1] The disease involves primarily the face and the trunk. Whereas, in immunocompetent adults it is usually limited to the genital area.[2] Atypical molluscum contagiosum requires a histopathological confirmation. Mutations in the dedicator of cytokinesis 8 gene (DOCK8) cause a combined primary immunodeficiency syndrome that is characterized by elevated serum IgE levels, depressed IgM levels, eosinophilia, sinopulmonary infections, cutaneous viral infections and lymphopenia. Distinguishing between DOCK8 deficiency and Job's syndrome, also referred to as autosomal dominant hyper-IgE syndrome, on clinical bases alone is challenging.

CASE REPORT

A 21-year-old boy presented with multiple, painless, flesh-colored and hyerkeratotic warty papules and nodules. They were located primarily on the face, forearms, trunk, back, lower limbs, buttock, groin and abdomen. (Fig. 1&2&3&4). Upon compression some of the papules released white caseous contents. Some lesions show central umbilication. The lesions started on legs around 2 years back. They had been treated with cryotherapy and topical salicylic acid with minimal effect. There after they recurred and spread systematically over time to involve most of the body and including the face. The patient did not report any incidence of similar lesions in his family members. The patient was diagnosed as primary combined immunodeficiency due to defect in DOCK 8 gene. He has the following disease related complications: recurrent sinopulmonary infection, bronchiecta-

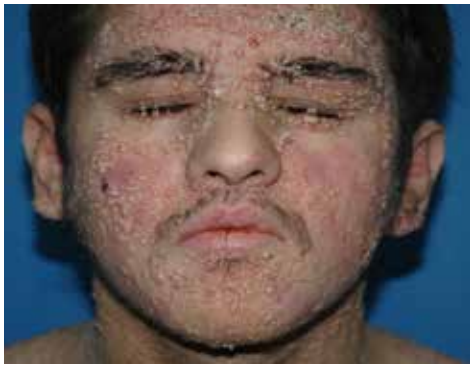

Fig. 1 Numerous shiny umblictated papules in face and neck.

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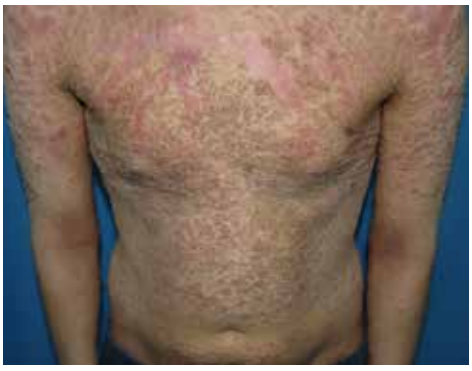

Fig. 2 warty papules and shiny umblicated papules as well as numerous stria rubra over ventral aspect of trunk and upper limb.

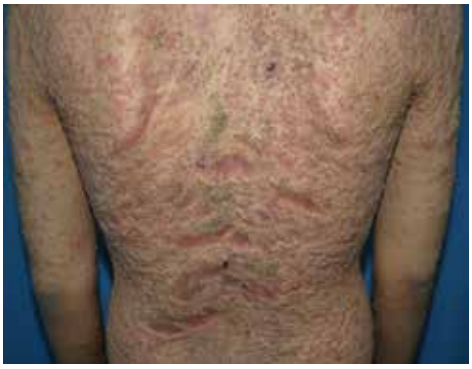

Fig. 3 warty papules and shiny umblicated papules in addition to numerous striarubra over dorsal aspect of trunk and upper limb.

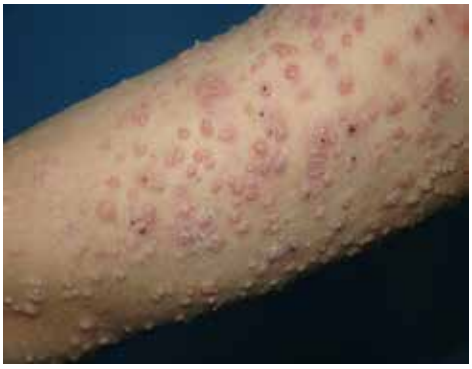

Fig. 4 Shiny umblicated papules in Rt thigh.

sis, high IgE, eosinophilia, eczema and the above mentioned skin lesions.

Local examination of the skin revealed well defined, dome-shaped, shiny, soft to firm flesh-colored papular and warty lesions on the face, forearms, trunk, back and abdomen. The lesions are variable in size. Hair, nails and mucous membranes showed no significant abnormalities. Laboratory investigations showed high IgE and eosinophilia.

We performed a whole excisional biopsyof one of the lesions. The specimen from the lesion showed lobulated endophytic hyperplasia with cup shaped invagination filled with molluscum bodies. molluscum bodies are large cells with cytoplasmic ,faintly granular eosinophilic inclusions that displace nuclei and contain viral particles (Fig. 5, 6).

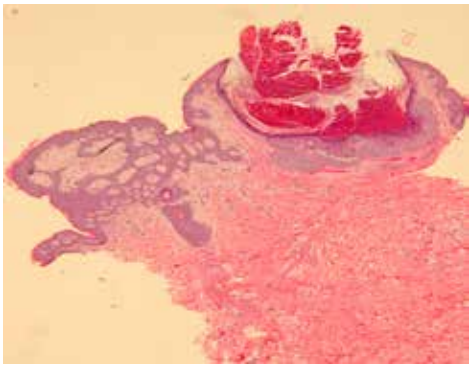

Fig. 5 Lobular endophytic epidermal hyperplasis with cup shaped invagination containing molluscum bodies.

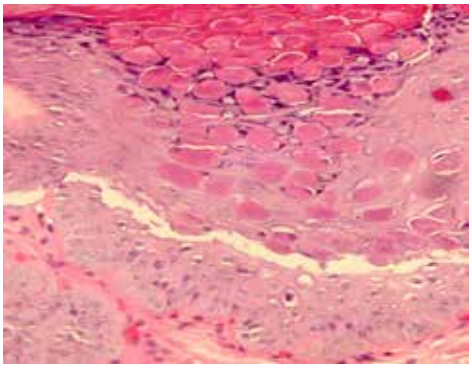

Fig. 6 Molluscum bodies within the cytoplasm of keratinocytes and pushing nucleus aside.

FINAL DIAGNOSIS

Disseminated Molluscum Contagiosum an a patient with Severe Combined Immunodeficiency due to defect in DOCK 8 Gene.

DISCUSSION

The appearance of Molluscum Contagiosum (MC) lesions in adult men requires an evaluation

of the immunocompromised state, but in children MC is rarely associated with immunodeficiency and usually no further evaluation is needed.[3]

DOCK8 is a member of the DOCK180-related family of atypical guanine nucleotide exchange factors (GEF) which interact with Rho GTPases.[4,5,15] Unlike the classical Dbl homology-pleckstrin homology (DH-PH) domain-containing GEF, DOCK180-related family members each have two related conserved protein domains. These protein domains are termed Dock Homology Regions (DHR). Whereas DHR2 contains the actual catalytic site for GEF activity, DHR1 is required for downstream signaling and biological function, probably through its ability to localize the enzyme complex to the plasma membrane. The presence of additional structural domains allows the 11 mammalian DOCK180-related family members to be grouped into four subfamilies.[5]

The DOCK-C (Zir) subfamily, which contains DOCK6, DOCK7, and DOCK8, is defined by the absence of additional domains besides DHR1 and DHR2. Prior to the discovery of DOCK8 mutations in the patients, DOCK8 had not previously been known to play a role within the immune system. Dock2-deficient mice have T cell lymphopenia, decreased cellularity of thymus and secondary lymphoid organs, loss of marginal zone B cells, decreased lymphocyte chemotaxis and migration, and decreased T cell proliferation due to impaired immunological synapse formation.[6,7,8,9] When backcrossed onto an allergy-prone genetic background, the Dock2-deficient mice spontaneously develop elevated serum IgE.[10]

However, the Dock2-deficient mice also have impairments in migration and other functions of neutrophils and plasmacytoid dendritic cells, including the ability of the latter to produce antiviral IFN-α in response to stimulation through toll-like receptors-7 and -9.[11,12,13,14] Thus, although the Dock2-deficient mice are similar to the DOCK8-deficient humans in their T cell lymphopenia and hyper-IgE, myeloid cell abnormalities seen in the mice are not obviously suggested by the clinical presentation of the patients. The function of DOCK8 is unknown, but by analogy to related molecules, the protein probably regulates cytoskeletal rearrangements that are required for cellular structure, migration, adhesion, and other functions.[16] The human DOCK8 gene, which consists of 46 to 48 exons, depending upon the isoform, is spread over ~250 kb on chromosome 9p24.3. DOCK8 was originally shown by Northern blot hybridization analysis to be expressed in various non-immune tissues such as placenta, kidney, lung, and pancreas.[15] However, DOCK8 is also highly expressed within the immune system, especially by lymphocytes, suggesting crucial functions in these cell types.[23]

The DOCK8 immunodeficiency syndrome accounts for subgroups of patients who have undefined combined immunodeficiencies or who were previously misclassified as having autosomal recessive Hyper-Immunoglobulin E Syndrome (HIES). Besides lymphopenia, DOCK8 deficiency has manifestations that have not previously been associated with HIES, including cancers related to cutaneous viral infections. Squamous-cell cancers was reported in some patients who had extensive human papillomavirus infections, and cutaneous T-cell lymphoma-leukemia was reported very rarely. Impaired CD8 T cells in DOCK8 deficiency suggests that these cancers may be due to impaired tumor surveillance. It is also possible that DOCK8 has tumor-suppressor functions. Indeed, DOCK8 deletions in primary lung cancers,

gastric- and breast-cancer lines, and gliomas suggest a role of DOCK8 in tumor suppression.[17,18]

DOCK8 deficiency exhibits an unusual constellation of clinical features, but diagnosis can be confusing when some features are absent. Both DOCK8 deficiency and classical hyper-IgE syndrome due to STAT3 mutations typically present with signs of atopic dermatitis, *Staphylococcus aureus* skin abscesses or soft tissue infections, pneumonias, elevated serum IgE, and eosinophilia. These two conditions may not be easily distinguished from each other during early childhood, as the non-immune manifestations unique to STAT3-mutant hyper-IgE syndrome, such as the characteristic facial appearance, pneumatoceles, delayed exfoliation of primary teeth, and pathological fractures, can take years to become evident.[19] As with hyper-IgE syndrome, other combined immunodeficiencies, such as the Wiskott-Aldrich syndrome, can be associated with eczematous rash, infectious susceptibility, and high IgE.[20] However, only DOCK8 deficiency is typically associated with asthma and severe allergies including anaphylaxis to foods. The most distinctive clinical feature useful in distinguishing DOCK8 deficiency from hyper- IgE syndrome and other conditions is the cutaneous viral infections. These infections are extensive, difficult to control, and often occur concurrently. The most common viruses involved are herpes simplex virus (HSV), human papillomavirus (HPV), molluscum contagiosum virus (MCV), and varicella-zoster virus (VZV). Chronic orolabial or ulcerative anogenital HSV infections, as well as herpes simplex keratitis and eczema herpeticum, are typically observed, but systemic HSV infections including herpes simplex encephalitis are not. Patients have disfiguring flat and verrucous warts from HPV infections, although it is unclear whether they are also at increased risk for genital warts. MCV lesions are often confluent, and VZV can present as severe primary infection or recurrent zoster. By contrast, sporadic cases of progressive multifocal leukoencephalopathy (PML) due to JC virus, and one case of systemic human cytomegalovirus (CMV) viremia, have rarely been reported.[21] The DOCK8 deficiency is associated with a variety of other types of infections. Patients have recurrent upper and lower respiratory tract infections, including otitis media, mastoiditis, sinusitis, pneumonia, and bronchitis. Unlike STAT3-mutant hyper-IgE syndrome, the pneumonias in DOCK8 deficiency are not primarily due to *Staphylococcus aureus,* but rather a wide spectrum of gram-positive and gram-negative bacteria and fungi. These include not only *Streptococcus pneumoniae* and *Haemophilus influenzae,* but also *Pneumocystis jirovecii* and Histoplasmosis. Aspergillosis, as occurs in STAT3-mutant hyper- IgE patients after parenchymal lung damage, has not been observed. Mucocutaneous candidiasis can occur in both conditions, although the overall frequency appears lower in DOCK8 deficiency. Cryptococcal, Listeria, pneumococcal, and *Haemophilus influenza* meningitis, as well as *Acinetobacter baumanii,* Klebsiella, and *Neisseria meningitides* sepsis, have been reported and can cause death.

DOCK8-deficient patients can also have recurrent infections of the gastrointestinal tract, such as Salmonella enteritis and Giardiasis. Together, the wide spectrum of infections and pathogens support deficits in both adaptive and innate immunity. In addition to atopy and increased susceptibility to infections, DOCK8 deficiency is associated with the development of malignancies in childhood or young adulthood. Squamous cell carcinomas, in

the setting of chronic cutaneous viral infections, as well as Burkitt or other lymphomas, predominate and contribute to fatalities. Microcystic adnexal carcinoma and leiomyoma have also been reported.[22] The occurrence of these cancers suggests a deficit in immune surveillance functions.

We reported this case of primary combined immunodeficiency due to defect in DOCK 8 gene.He had recurrent sinopulmonary infection, Bronchiectasis. high IgE, eosinophilia, eczema and disseminated molluscum contagiosum.

The viral infections of the skin are extremely difficult to manage in DOCK8-deficient patients. Because *Staphylococcus aureus* skin infections can worsen the eczema and trigger eczema herpeticum, patients benefit by decreasing colonization through the use of bleach baths, topical antiseptics, or antimicrobials. Corticosteroids can also be used to control eczema, but can potentially worsen viral infections, and when discontinued the eczema can flare. Valacyclovir or acyclovir is usually given to contain herpes simplex virus outbreaks. Topical imiquimod, cidofovir, and other conventional treatments for warts and molluscumcontagiosum may be tried but are usually unsuccessful. Interferon-α has anecdotally helped to control warts and molluscum contagiosum in some patients.[23] Those patients who have impaired functional antibodies may benefit from intravenous immunoglobulin infusions to decrease the frequency of sinopulmonary infections. However, the immunoglobulin infusions do not affect the viral infections, which is consistent with findings that patients already have protective titers to HSV or VZV. This genetic deficiency is associated with high morbidity and mortality.[32] Reported patients were confirmed to have DOCK8 mutations on both alleles, 7 of them died between the ages of 6 and 21.[21,23,24] 3 patients of these 7 patients died from malignancy (squamous cell carcinomas, T cell leukemia-lymphoma), and 4 died from either infections (sepsis, encephalitis, PML) or CNS vasculitis. The difficulty in controlling viral infections – and their likely contribution to increased risk of skin cancers – has been an argument for hematopoietic cell transplantation. Indeed, two DOCK8 patients were retrospectively found to have undergone myeloablative and reduced intensity conditioning followed by allogeneic hematopoietic cell transplantation (HCT).[24] They are now up to four years out of transplantation with complete and stable engraftment, as well as near normalized lymphocyte functions and completely resolved molluscum contagiosum and recurrent herpes zoster infections. DOCK8 is expressed at low levels in non-immune tissues and its loss in various cancers suggests that DOCK8 could act as a tumor suppressor molecule, apart from its probable role in CD8 T cells for tumor surveillance.[25,26,27,28,29] Therefore, it remains to be seen in long-term follow up whether transplantation is completely curative in preventing malignancies. Furthermore, as is the case for other combined immunodeficiencies, the variable outcome makes it is difficult to predict natural history in less severely affected individuals. For example, two patients who only had infectious complications of their disease, without malignancy, are still alive in their 40's.[21] Together, these results indicate that HCT should be strongly considered in severe cases of DOCK8 deficiency, but it remains unclear as to its place in less severely affected individuals.

We reported this case of disseminated molluscumcontagiosum in a patient with primary combined immunodeficiency due to defect in DOCK 8 gene for the rarity of the condition which we believe is

under-reported because of lack of awareness.

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