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CASE REPORT

Coexistence of atopic dermatitis and thrombocytosis: diagnostic odyssey: a case report

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ABSTRACT

Background: Atopic dermatitis (AD) is one of the most common diseases encountered in pediatric practice. Genetic factors play a role in the development of this condition. Topical corticosteroids are the cornerstone of AD management, but with potentially serious adverse events. Misuse of these medications is not uncommon.

Case Presentation: We describe a case of severe AD with inadvertent overuse of topical steroids. The patient presented with multisystem involvement and a cushingoid appearance. Laboratory tests showed thrombocytosis and abnormal liver function test, among other findings. A whole exome test showed mutations in two genes, a homozygous pathogenic variant c.317C>T p.(Pro106Leu) in the protooncogene, thrombopoietin receptor (*MPL*) gene (NM_005373.2) inherited from both parents and a de novo heterozygous c.139C>T p.(Arg-47Cys) in the *CARD11* gene (NM_001324281.1), that explain her combined presentation.

Conclusion: The aim of this report is to share our experience with the diagnosis and treatment of a challenging case. This report also shows the association between the *MPL, CARD11* genes, and severe AD. In addition, this case is consistent with the published literature on systemic involvement in severe AD and variable response to routine management.

Keywords: Atopic dermatitis, *MPL*, thrombocytosis, *CARD11*, whole exome sequencing.

Background

Atopic dermatitis (AD) is one of the most common diseases in pediatric practice. AD is an inflammatory disease often associated with other IgE-mediated diseases. It can affect any age but usually manifests in infancy with dry skin, eczematous lesions, and, if chronic enough, lichenification (1). AD is the most common chronic skin disease. In a worldwide survey conducted in over 18 countries, the reported AD in children ranged from 13.5% to 41.9%, and in Saudi Arabia, it was as high as 41.7% (2). Genetic factors play a role in the development of AD. The probability of developing AD or other atopy is more than 50% and 80%, respectively, if one or both parents have atopy. The-loss of-function mutations within filaggrin (*FLG*) gene (**Fil**ament **Ag**gregating Prote**in**) have been identified in 30% of patients. *FLG* is a protein that acts as a natural moisturizing factor in the epidermis. This fact indicates the role of dryness in the pathological process of the disease. In addition, *FLG* helps to keep the outermost layer of skin, the corneocytes, together, forming an effective barrier against pathogenic microbes. Therefore, patients with AD have a higher risk of developing superimposed infections at the affected areas (3).

The various associations with AD make diagnosis difficult in some cases. Recent studies have shown associations between AD and a number of multi-organ and systemic disorders (e.g., cutaneous infections, sleep disorders, and cardiovascular risk factors) with combined effects of skin-barrier disruption, immune dysregulation, and iatrogenic such as corticosteroid use complications

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(4). Fatty liver occurs concomitantly with AD in a significant percentage. An increased incidence of fatty liver has been reported in healthy non-obese children. The prevalence of fatty liver increased annually, reaching 12.5% in nonatopic children, 13.1% in patients with bronchial asthma, 13.7% in patients with allergic rhinitis, and 33.9% in patients with AD (4).

In some patients, a broad phenotypic spectrum or atypical presentation may be the result of monogenic disorders or co-occurrence of two suspected monogenic diseases (5). At present, the advanced genetic testing methods of next-generation sequencing (NGS) such as whole-exome sequencing (WES) and whole-genome sequencing play an important role in the diagnosis of various diseases. It is increasingly contributing to strategic diagnostic evaluation, especially in atypical clinical scenarios and in many cases solves the diagnostic odyssey (6).

Inherited loss-of-function mutations of the thrombopoietin receptor (also known as the protooncogene, thrombopoietin receptor (*MPL)* gene OMIM #159530) are frequently associated with severe thrombocytopenia and aplastic anemia. In contrast, a recent study observed a confirmed *MPL* mutation in 26 children with familial thrombocytosis in the Saudi population (7). While homozygous null mutations in *CARD11* (OMIM #617638) lead to immunodeficiency-11B with AD, heterozygous gain of function mutations lead to selective B-cell lymphoproliferative disorders (e.g., B-cell expansion with nuclear factor kappa B subunit 1 and T-cell anergy. In addition, the gene has also been identified as a risk locus for AD; however, there is no overlap in the function of these two genes (8).

In this paper, we report a case with severe AD and thrombocytosis. Using NGS we diagnosed her with two genetic mutations involving *MPL* and *CARD11* gene mutations. The case is thought to be unique because it is associated with the above genes in addition to the other systemic manifestations.

Case Presentation

A 12-month-old girl who had suffered from chronic eczema since 4 months of age was called to the emergency department after routine screening at a dermatology clinic because of abnormal laboratory results of severe thrombocytosis [1,206 × 109/l (150 ~ 450 × 109/l)]. The patient was delivered by cesarean section in breech presentation. Her birth weight was 3 kg. She was exclusively breastfed and received vaccinations at the proper time for up to 9 months. She has no known allergies to food or medications; however, the mother noticed a flare-up of lesions when she ate peanuts. She is the first-born child of consanguineous, healthy parents in their 30s. There is family a history of AD, allergic rhinitis, asthma, and an aunt who has breast cancer. The patient was treated with topical mometasone furoate 0.1% cream [group 4 potency] for eczematous lesions. However, it had been misapplied daily as a moisturizer all over her body for about 10 months.

On examination, the patient was noticed with cushingoid features, a swollen face, and fatty limbs. She was pale with a yellowish discoloration of the sclera. An eczematous rash extended over her face, hands, abdomen, and perioral and perianal areas (Figure 1). She has alopecia with sparse hair of abnormal brown color. She has stunted growth as her height was below the 3rd percentile while her body mass index was above the 95th percentile. Vital signs were within normal ranges for her age. The rest of the examination is unremarkable.

In addition to the severe uncontrolled eczema and steroid toxicity, she was diagnosed with severe malnutrition, as she was exclusively breastfed and consumed very little. Echocardiography ruled out cardiomyopathy secondary

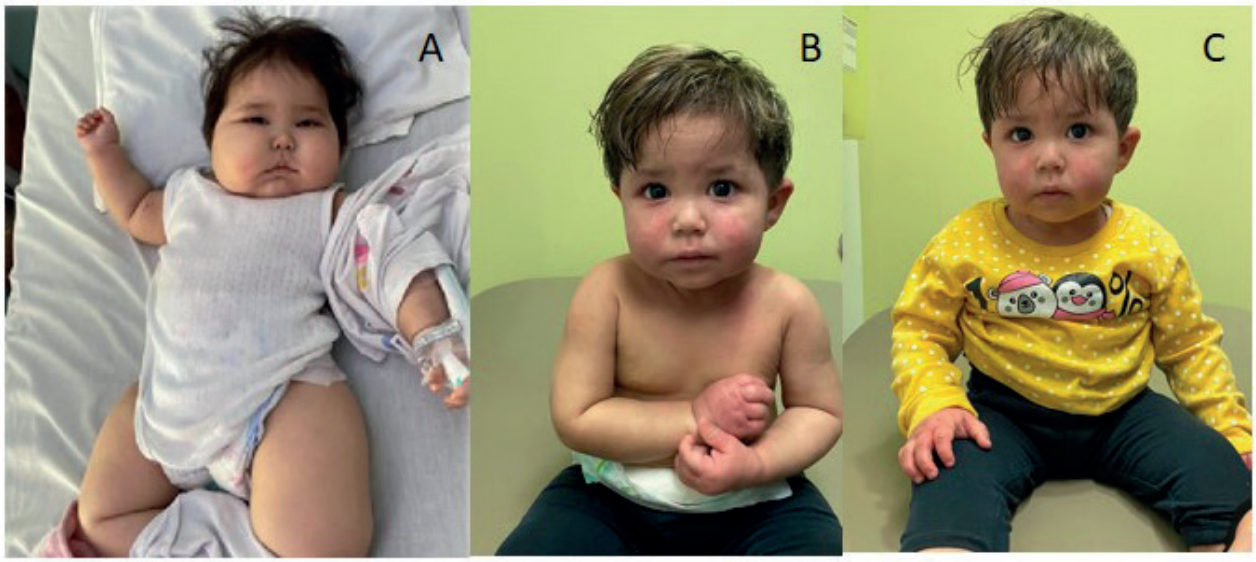

Figure 1. *(A) patient at presentation with typical cushingoid appearance, (B) patient with interval improvement of external cushingoid features at follow-up after 5 months, (C) note the erythematous eczematous rash over cheeks and hands.*

to malnutrition. The patient was started on nasogastric fed with caloric intake gradually increased to avoid refeeding syndrome. A *potent topical corticosteroid*, Mometasone Furoate, was replaced with 1% hydrocortisone and Protopic ointment, in addition to frequent application of moisturizing petrolatum. She was also treated with zinc sulfate, ferrous sulfate, multivitamin A, D, E, and K, and ursodeoxycholic acid and cholestyramine-l for cholestasis. The mother was informed in detail about the risk of adrenal suppression and the indication for a stress dose of hydrocortisone was explained to her. She was educated in detail about skin care and types of steroids.

Over the course of several months, out-patient department follow-up showed significant improvement in her nutritional, developmental, and skin condition. Her cholestasis resolved and ursodeoxycholic acid and cholestyramine were discontinued. Platelet levels never normalized, and she continued to have persistent thrombocytosis.

Method

Laboratory tests

Laboratory tests showed severe thrombocytosis, leukocytosis, and microcytic hypochromic anemia with reticulocytosis. Liver function tests revealed direct hyperbilirubinemia 119.1 (~8.6 umol/l) with high alkaline phosphtase 531 (156-369 U/l), and gamma-glutamyl transferase 65.8 (9-36 U/l) levels, hypoalbuminemia 20-22 (38-54 g/l). Cortisol levels, adrenocorticotropic hormone and lipid profile were in the acceptable range. No evidence of biochemical dysfunction of hypothalamic-pituitary-adrenal axis hormones was found. Examination for viral and autoimmune hepatitis was negative.

Ultrasound revealed hepatomegaly with evidence of fatty liver. Urinalysis suggested urinary tract infection and culture grew >100,000 cfu/ml *Escherichia coli*, with high C-reactive protein 55 (~8 mg/l), also culture of erosive eczematic lesions grew *Staphylococcus aureus*, but the result herpes simplex virus polymerase chain reaction result was negative, after which she received a treatment course with ciprofloxacin. Further testing for immunodeficiency disorders was performed, which showed a significantly elevated of total IgE level of 103 (<3.2 KU/l), whereas IgG 4.83 (7.51-15.60 g/l), IGA 0.97 (0.82-4.53 g/l), and IgM 0.41 (0.46-3.04 g/l) were normal. In addition, lymphocyte subset analysis showed slightly increased expression of CD25 in 8% (2%-5%) of total T cells; otherwise, expression of all other markers was within normal values consistent with patient age, including CD4 and natural killer cells. A hair biopsy was obtained and showed trichorrhexis nodosa.

Whole exome sequencing

The generated library is sequenced on an Illumina platform to achieve an average coverage depth of ~100×. Typically, ~97% of the target bases are covered >10×. An end-to-end in-house bioinformatic pipeline was used including base calling, alignment of reads to GRCh37/hg19 genome assembly, primary filtering out of low-quality reads and likely artifacts, and subsequent annotation of variants. The evaluation focuses on the coding exons as well as the flanking ±20 intronic bases. All inheritance patterns were considered. In addition, the provided family history and clinical information were used to evaluate the identified variants. The WES showed mutations in two genes, a homozygous pathogenic missense variantc.317C>T p.(Pro106Leu) in the *MPL* gene NM_005373.3, NP_005364.1 inherited from both parents, this variant has previously been described as disease causing for thrombocytosis. On other hand another de-novo heterozygous c.139C>T p.(Arg47Cys) missense variant of unknown significant was detected in the *CARD11* gene NM_032415.7, NP_115791.3. This mutation as along with other truncating variants was missing from a large-scale exome sequencing database such as Exome Aggregation Consortium, dbSNP/1,000 genome or Exome Sequencing Project, and the Genome Aggregation Database. In addition, this variant, along with other truncating variants, was absent from 2,000 ethnically matched controls in the local database. Both mutations were confirmed by Sanger in CAP-accredited laboratory.

Discussion

AD is known to be associated with a loss-of-function mutation in the *FLG* gene, leading to a decrease in FLG protein and consequent in barrier defect (3). Review of the literature revealed reports of successful use of 0.03% topical tacrolimus (TCs) in the treatment of certain types of dermatitis such as granuloma gluteale infantum and isolated lip dermatitis (atopic cheilitis) (9). Because the patient did not respond adequately and satisfactorily to the topical steroids previously used to control the flare-up of eczema, the patient was treated with TCs ointment 0.03% which resulted in significant improvement.

While IgE and T cells are the main mediators in the pathogenesis of AD, some studies have shown an opposed effect of mast cells. Hershko et al. (10) identified a protective role of mast cells against chronic eczema mediated by IL-2, which suppresses chronic allergic reactions. This finding may be related to the severe eczema observed in the reported case.

Caspase recruitment domain (CARD)-containing membrane-associated guanylate kinase proteins from a family of three scaffold proteins that are highly conserved in amino acid sequence, including CARD11/CARMA1 (CARMA1) (11). Recent evidence has shown that CARD proteins mediate the induction of an inflammatory response in keratinocytes and that mutations in the encoded genes segregate with familial transmission of chronic inflammatory diseases of human skin through the formation of a trimeric complex comprising BCL10 and MALT1 proteins (12). In recent decades, the formation of the CARD11-BCL10-MALT1 (CBM) signalosome complex has emerged as an essential step in the regulation of NF-KB in lymphoid immune cells (13). A *CARD11* gene mutation has been found to interact with BCL10 and promote NF-KB activation resulting in an autosomal dominant immunodeficiency type 11B with AD. Recent reports indicate that *CARD11* is also associated with

several immune-related diseases and traits, including multiple sclerosis, eczema, thrombocytopenia, and susceptibility to Kawasaki disease due to impaired B-cell development and B-cell function (9,14)

Much research is still needed to improve our understanding of the relationship between AD and many associated conditions. To date, there has been no report about the relationship with the *MPL* and *CARD11* gene. Although there is no specific management for these cases, patients are treated with supportive treatment, however, proper genetic counseling, the introduction of newborn screening programs and parenteral diagnosis can play a major role in reducing the burden of such severe disorders (15). This can be accomplished by prenatal genetic testing for monogenetic disorders (PGT-M). PGT and *in vitro* fertilization are options for parents wishing to have future pregnancies (16,17).

This report demonstrates the utility of early genetic testing in resolving diagnostic dilemmas and prompt treatment. As evident in this case, genetic testing has drawn attention to that fact that despite the typical clinical presentation of eczema, the patient has a genetic defect that would explain the persistent thrombocytosis. Whether or not these genetic defects are related to the failure to respond to high-potency steroids, even when inappropriately overdosed is still uncertain.

Conclusion

This case demonstrates the potential adverse effects of inappropriate use of TCs. Another lesson from this study is that genetic testing is appropriate in the setting of a systemic manifestation in addition to a chronic persistent AD. This report aims to sensitize pediatricians to the role of testing for underlying genetic pathologies in some disorders where typical treatment proves ineffective. Therefore, timely ordering of genetic testing is an essential step in patient care in such situations.

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Consent for publication

Due permission was obtained from the parents/guardians of the patient to publish the cases and the accompanying images.

Ethical approval

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions
F.M. and A.A. conceptualized the work. F.M. and M.A. drafted this manuscript. F.M., M.A., L.A., K.A., R.A., and A.A. revised this manuscript. F.M. and A.A. were involved in the clinical management of the patient and all authors read and approved the manuscript for submission.

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