Germline CBM-opathies: From immunodeficiency to atopy

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Learning objectives: “Germline CBM-opathies: From immunodeficiency to atopy”
1. To better understand the clinical presentation and implications of germline CBM-opathies.
2. To review optimal evaluation and management of a broad spectrum of human diseases categorized under germline CBM-opathies.

CME items

Question 1. A 4-month-old exclusively breast-fed infant presents for initial evaluation of severe atopic dermatitis. Family history is notable for allergic rhinitis and asthma in both parents and peanut allergy in an older sibling. Parents have been treating with topical application of coconut oil but note no improvement. Mutations of which gene are associated with this clinical presentation and could explain the infant’s symptoms, and what initial management strategy should be used?

A. BCL10, skin care optimization, and systemic corticosteroids
B. CARD9, skin care optimization, and dupilumab
C. CARD9, skin care optimization, and topical corticosteroids
D. CARD14, skin care optimization, and topical corticosteroids

Question 2. A healthy-looking newborn with severe deficient T- and B-cell function is identified to have biallelic loss-of-function mutations in a single member of the caspase recruitment domain (CARD) protein–B cell CLL/lymphoma 10 (BCL10)–MALT1 paracaspase (MALT1 [CBM]) complex, resulting in complete abrogation of nuclear factor κB (NF-κB) signaling. The most appropriate therapeutic approach is —

A. intravenous immunoglobulin (IVIG).
B. IVIG and a TNF-α inhibitor to control psoriatic lesions.
C. IVIG, trimethoprim-sulfamethoxazole prophylaxis, and immediate referral for consideration of hematopoietic stem cell transplantation.
D. IVIG, rituximab, corticosteroids, and acyclovir to control EBV.

Question 3. A 2-year-old boy from a consanguineous relationship presents with recurrent gastroenteritis and colitis, which began at 12 months of age. In addition, he has a history of multiple respiratory syncytial virus infections, recurrent otitis, and oral candidiasis beginning in the first year of life. Laboratory studies are notable for diminished IgG, IgA, and IgM levels. Flow cytometry demonstrated diminished numbers of memory B and T cells in addition to diminished numbers of regulatory T cells. T cells demonstrated decreased proliferation on mitogen stimulation. On further examination, his fibroblasts show markedly reduced NF-κB activation after LPS, zymosan, and polyinosinic-polycytidylic acid stimulation. Which of the following genetic lesions have been associated with frequent viral, bacterial, and fungal infections in infancy?

A. biallelic BCL10 loss-of-function mutations
B. biallelic CARD9 loss-of-function mutations
C. CARD11 gain-of-function mutation
D. CARD14 hypomorphic mutation
Question 4. A 26-year-old woman presents with 1 year of plaques and nodules on her face and neck. The lesions are erythematous with a dark serpiginous border. Fungal cultures grew *Phialophora verrucosa*. Her medical history is notable for recurrent oral candidiasis. HIV test results are negative. IgE levels are increased, and peripheral eosinophilia is present. Immune response to vaccines is normal, and flow cytometry shows normal numbers of natural killer cells and T and B lymphocytes. This presentation is most characteristic of which germline mutation?

A. heterozygous gain-of-function mutation in *CARD11*
B. homozygous loss-of-function mutation in *CARD9*
C. null mutation in the α chain of the IL-2 receptor
D. single-codon frameshift deletion in signal transducer and activator of transcription 3 (*STAT3*)

Question 5. A 2-year-old boy presents for evaluation after a prolonged hospitalization for EBV infection. His mother reports a history of several upper respiratory tract infections and several episodes of molluscum contagiosum. Physical examination is notable for splenomegaly. Initial workup reveals mildly decreased IgG and normal IgA and IgM levels; a normal polyclonal gamma component in serum electrophoresis; increased total B-cell counts with low class-switched memory and normal T-cell and natural killer cell counts on flow cytometry; 5 of 23 protective pneumococcal, normal H influenza, and low tetanus vaccine titers; and impaired proliferation to mitogens and antigens. The diagnosis of B-cell expansion with NF-κB and T-cell anergy (BENTA) has been associated with which of the following?

A. heterozygous gain-of-function point mutation in the LATCH domain
B. heterozygous loss-of-function point mutation in the CARD domain
C. homozygous deletions in the guanylate kinase–like domain leading to truncated protein
D. normal *CARD11* sequencing