

Chronic mucocutaneous candidiasis

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Case study

- Boy, born 1994, 9th pregnancy, 3 siblings, all healthy, no consanguinity, ID, sudden deaths...
- Pregnancy and delivery normal
- Recurrent oral candidiasis since 2nd week, + skin lesions, since 3rd month on oral antimycotics, prokinetics, „his typical signs“ – constipation, meteorism, oral candidiasis
- Referred to our dept. at 10,5 months, repeated admissions due to exacerbation of candida or bacterial infections during the first 2 years of life

Case study

- CBC + diff., lymphocyte subpopulations normal, normal levels of Ig + subclasses, spec. Ig to HI, tet toxoid, pneumococcus, biochemistry normal, CMV, EBV, HSV negative, metabolic disease screening negative, thyroid fx normal
- Repeated *Candida albicans* cultures, well sensitive
- Thriving well, 3-5 respiratory illnesses per year

Case study

- Slightly decreased INT, phagocytosis on first admission, later normal burst test
- Negative Ab to Candida repeatedly
- Normal PHA, PWM stimulation response, diminished candidin stimulation response
(Institute of Immunology, Motol, Prague)
- Cytokine production tests not done

Case study

- Permanent antimycotic prophylaxis – nystatine, fluconazole (50 mg/day) + lactulose, prokinetics, loratadine
- Worsening of GI symptoms during acute illnesses, no skin/nail lesions since first year
- No clinical or laboratory signs of adrenal insufficiency, hypoparathyroidism or other autoimmunity

Case + questions – pediatrician view

- Chronic mucocutaneous candidiasis ✓
- APECED/APS-1 ?
Familial chronic mucocutaneous candidiasis without endocrinopathy, FCMC with hypothyroidism, FCMC with ICAM-1 deficiency, chronic localised candidiasis, candidiasis with hyper-IgE syndrome, CMC with thymoma, candidiasis with chronic keratitis, chronic oral candidiasis ... AR / AD / unknown inheritance (Zuccharello et al. J Med Genet 2002;39:671–675)
- How aggressive should we be in search of other APECED components, what tests (ACTH level + ACTH stimulation test vs. cortisol level)

Case + questions – pediatrician view

□ Should we search for mutations ?

... is there genotype – phenotype correlation ?

not yet established, but typical mutations (Finnish, British, Jewish) cause different AIRE functional impairment... (The autoimmune regulator: a key toward understanding the molecular pathogenesis of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy – Meriluoto et al., Keio J Med 50 (4): 225–239, December 2001)

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7 y boy w/ hypoparathyroidism, dysmorphic face, PMR, R257X/wt

15 y boy w/ recurr. infections, CMC, R257X/wt, mother same, healthy

14 y girl w/ alopecia areata, nail dystrophy, eufunctional goiter w/ anti-TG, anti-TPO Ab+, V484M/wt, mother same, healthy

(Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Syndrome: Time to Review Diagnostic Criteria? – Buzi et al. J Clin Endocrinol Metab 88: 3146–3148, 2003)

→ how come ?



Pediatrician-interested-in-immunology view

□ Is AIRE mutation sufficient to cause an APECED-spectrum disease ?

→ thymus microstructure influence on AIRE expression — RelB-deficient mice: irregular thymic architecture, activated MHC medullary epithelial cells absent also lack Aire expression + have an increased number of autoreactive T cells in the peripheral blood — impaired

negative selection in the thymus (Zuklys S et al.: Normal thymic architecture and negative selection are associated with Aire expression, the gene defective in the autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). J Immunol 2000; 165: 1976–1983)

Pediatrician-interested-in-immunology view

→ AIRE in Omenn (monogenic (?) immune dysregulation model) ... AIRE expression after HSCT (SCID repopulating mice ?) ... fetal thymus organ culture (FTOC) with the use of RNA-interference

Thank you for your attention !