ADA2 Deficiency Complicated By EBV-driven Lymphoproliferative Disease

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Introduction

ADA2 deficiency was first reported in 2 parallel publications in 2014 in association with polyarteritis nodosa, vasculopathy and early-onset stroke [1,2]. The clinical phenotype has since expanded to include immune deficiency without vasculopathy, cytopaenias, enteropathy, red cell aplasia, lymphadenopathy, splenomegaly and hepatomegaly. The range of severity and heterogeneity of presentation is highly variable, even with in patients with the same variant or members of the same family. Scheep et al. screened 181 antibody deficient patients and found ADA2 deficiency in 9 [3]. This is the first reported case of ADA2 deficiency complicated by EBV-driven lymphoproliferative disease.

Patient/Pedigree

We report a 29-year-old male, third child of non-consanguineous parents, with microcytic anaemia, neutropaenia and recurrent infections in infancy including skin infections (Staphylococcus aureus and Streptococcus pneumoniae), respiratory tract infection (RSV, Haemophilus influenzae and Streptococcus pneumoniae) and herpetic mouth ulcer. Age 6 his immunoglobulins, B-cells and CD4 T-cells were low and immunoglobulin replacement was commenced. He remained well until he presented age 29 with a two-week history of fatigue, sore throat and fever. EBV-driven lymphoproliferative disease was diagnosed and treated with chemotheraphy and allograft. EBV became undetectable. Complications included CMV reactivation, severe hepatic veno-occlusive disease and failure to engraft. A repeat allograft engrafted successfully but he had multiple infections and died.

Discussion

ADA2 is predominantly expressed by monocytes and other cells of the myeloid lineage. It converts adenosine to inosine and deoxyadenosine to deoxyinosine. It has approximately 100-fold lower affinity for its substrates than ADA1 (mutations in which cause a SCID phenotype). It also differs from ADA1 in being predominantly secreted rather than intracellular and in the cell types it binds. ADA2 is most active at acid pH and is therefore thought to have a role in sites of inflammation and tissue hypoxia [4]. This is the first description of EBV-driven lymphoproliferative disease in ADA2 deficiency. Primary immune deficiencies manifesting as severe EBV-induced disease are associated with mutations in genes including SH2D1A, XIAP, ITK, MAGT1, CORO1A, CD27, CD70, NFKB1 and RASGRF1 [5]. These genes all code for proteins that are involved in the interaction between CD8+ T cells and B cells and/or intrinsic T cell signalling pathways. EBV susceptibility is also a feature of monogenic NK cell disorders including CD16 deficiency, MCM4 deficiency and GATA2 deficiency. High serum ADA2 activity has been detected in a number of infectious, inflammatory and malignant diseases but was particularly increased in infectious mononucleosis [6]. In addition to its enzymatic role in purine metabolism ADA2 can act as a growth factor. ADA2 is reported to increase CD4+ T cell proliferation, with ADA2 having increased effect in the context of low monocyte concentration [7]. Deficiency of ADA2 may also have indirect effects as ADA2R receptors are present on most immune cells. Adenosine binding at ADA2R Gs protein-coupled leads to reduced T cell activation, TCR-signalling and reduced cytotoxic activity of CD8+ T cells and NK cells [8]. AdaR small molecule inhibitors are being investigated for cancer immunotherapy [9]. Other environmental or genetic factors may have played a role in the development of EBV-driven lymphoproliferative disease in this patient but this case raises the possibility that ADA2 deficiency is another primary immunodeficiency that causes susceptibility to severe EBV-induced disease.

Conclusions

ADA2 deficiency has highly variable severity and a broad ranging clinical phenotype including EBV-driven lymphoproliferative disease. Monitoring of EBV viral load should be considered in this condition.