Atypical Presentation of Adenosine Deaminase Deficiency ADA2 Deficiency

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Abstract

Here we report on a challenging diagnosis of VIAHS in a patient who presented at a very early age with a perianal abscess with fistula formation, fever, aphthous ulcers, bicytopenia, and hematochezia. Marked phenotypic variability can occur, and screening for families should be initiated in those with ADA2 mutation.

Atypical Presentation of Adenosine Deaminase Deficiency ADA2 Deficiency

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Keywords:

ADA2, autosomal recessive vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome(VIAHS)

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Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy (Informed consent attached in online submission)

Key Clinical Message:

Here we report on a challenging diagnosis of a VIAHS patient who presented with atypical clinical features of perianal abscess with fistula formation, fever, aphthous ulcers, bicytopenia, and hematochezia at a very early age of disease onset. This case highlights the consideration of ADA2 deficiency as a differential diagnosis of enlarging cutaneous abscess with no evidence of wound healing in the setting of leukopenia and neutropenia.

Background:

Autosomal recessive vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome (VIAHS) is a rare autosomal recessive disease caused by biallelic mutations in ADA2 (formerly known as Cat Eye Syndrome candidate region 1, or CECR1) [1-2]. The most prevalent mutation in the first reports of Adenosine deaminase deficiency (DADA2) was the p.Gly47Arg variant. However, more than 60 disease-causing variants, mostly missense single-nucleotide variants, and some splicing variants have now been described [3-4] across the entire coding region of ADA2 some of which are shown (Figure 1).

The ADA2 locus contains variability amongst humans, resulting in polymorphic variations associated with DADA2 [5]. The manifestation of VIAHS varies greatly amongst children and adults, including those homozygous for the same founder mutation, in the form of varying ages of presentation and variability of symptoms and severity [5-6]. Autoinflammatory characteristics constitute periodic fevers, musculoskeletal involvement, rashes (livedo racemosa/ reticularis) [4-7]. Vasculitis, usually manifested before ten years of age, appears as ischemic/hemorrhagic strokes or cutaneous polyarteritis nodosa (PAN), which remains a predominant feature in most cases described to date [7]. Dysregulation of immune response may manifest as autoimmunity, bone marrow deficiencies, and lymphadenopathy. Hematologic defects can include any cytopenias of a cell line defect to pancytopenias [4-7]. Gastrointestinal manifestations include hepatosplenomegaly, abdominal pain, and inflammatory bowel disease in up to 10% of patients. Other manifestations may include hypertension, hepatosplenomegaly, and neurological defects [7-8].

Here we report on a challenging diagnosis of VIAHS in a patient who presented at a very early age with a perianal abscess with fistula formation, fever, aphthous ulcers, bicytopenia, and hematochezia.

Case presentation:

Patient X is the index case, previously healthy 18 months old female, the first child of healthy Saudi consanguineous parents, presented to our Emergency Department with a five-day history of high-grade fever, associated with diarrhea development lethargy, an anal lesion. Fever reached a Tmax of 39 Celcius and was partially responsive to antipyretics. Family History was positive for two childhood deaths at two years of age, with fever of unknown origin from the paternal side. One family member on the paternal side required intravenous immunoglobulin with an unknown cause—positive maternal family history of Behçet's disease.

Physical Examination revealed a normal child with no findings apart from the presence of oral aphthous ulcers along buccal mucosa and an anal lesion, described to be 1cm x 1cm regular erythematous painless papule. The child underwent diagnostic workup and the initial investigations showed neutropenia and leukopenia, with white blood count (WBC) 4.58 10e9/L (reference range 4-11 10e9/L), ANC: 0.13 10e9/L, Hemoglobin: 10 g/dl, Platelet 154 10e9/L. Inflammatory markers showed increased CRP 148, ESR 120. Blood, urine, and cerebrospinal fluid cultures were negative.

Throughout her hospital stay, fever persisted at four hourly intervals reaching a T max of 40 Celsius for three months. Anal lesion progressed to enlarge and was complicated by cutaneous perianal fistula formation at 2'oclock and 9oclock position associated with exudative discharge. Exudative discharge grew Pseudomonas and Escherichia coli. Multiple Aphthous ulcers proceeded to develop in oral mucosa; oral scrapings showed growth of candida tropicalis. Diarrhea progressed to include hematochezia and blood clot passage requiring multiple blood transfusions.

The patient continued to be persistently neutropenic 0 - 0.35, leukopenic 0.22- 4.92, with thrombocytopenia development. Inflammatory markers remained elevated CRP 310 – ESR 120 ferritin 15141. The coagulation profile remained normal. Antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) were negative. Immunoglobulin levels IgG 3.87 (2.9-10.7 g/L), IgA 0.28 (0.40-1.20) and IgM 0.2 (0.3-1.5) remained unaffected along with post-vaccination titers. Oxidate burst test was resulted negative. Extensive workup for virology, fungemia, and mycobacterium all remained negative. C3 and C4 complement factors were within the normal range.

The perianal abscess was complicated by growth in size; and failure of formation of granulation tissue.

Initially, stool for occult blood resulted positive, with the development of microcytic hypochromic anemia. Abscess depth progressed to involve vascular beddings resulting in hematochezia and fresh blood passage. Hemoglobin reached a low of 4mg/dl, requiring multiple blood transfusions and fresh frozen plasma (FFP). The Source of bleeding was not identified on a clinical basis. Mickell's scan resulted in being negative as well as RBC technetium scan. Ultrasound was done, which was negative for intussusception and organomegaly. Endoscopy, and colonoscopic findings from the rectum to ascending colon were normal.

Intervention for neutropenia included methylprednisolone 10 mg/kg and intravenous immunoglobulin therapy with no response. A trial of Granulocyte colony-stimulating factor (GCSF) was initiated. She received a continuous infusion of GCSF 200 units for one month, with a lack of response. Furthermore, a trial of Human Leukocyte antigen typing was performed on both parents for future bone marrow transplant (BMT).

Bone Marrow Aspiration was performed, showing hypocellular bone marrow (50% cellularity), myeloid aplasia and extensive histiocytic proliferation with significant hemophagocytosis. Flow cytometry was performed on bone marrow aspirate showing severe lymphocytopenia (absolute including all lymphocyte subsets (B-,T-, NK-). The overall findings suggestive of primary or secondary immunodeficiency due to bone marrow suppression.

Blood passage was daily with the presence of clots; about 50 ml. At the time, fever continued, and tachycardia developed to reach a heart rate of 200 bpm. The patient was admitted under the care of the Pediatric Intensive Care Unit (PICU). Platelets declined to reach 1, despite multiple trials of platelets transfusion, as well as continuous infusion. After a multi-disciplinary meeting was conducted (involving general pediatrics, immunology, hematology-oncology, infectious diseases, gastroenterology, Rheumatology, Pediatric surgery, Pathology, PICU), it was agreed upon to initiate a trial of Anakinra 10 mg/kg interleukin (IL-1 receptor agonist); fever subsided for two days and resumed. A chimeric monoclonal antibody, infliximab, was given with no satisfactory outcome.

Whole Exome Sequencing demonstrated a homozygous pathogenic variant of the ADA2 gene suggesting VIAHS. Persistent massive peri rectal bleeding and tachycardia continued for a duration of two months. Cardiac ejection fraction was reduced; she was started on inotropic support and supportive management. She proceeded to develop acute kidney injury, liver injury with abdominal distention. Respiratory status declined secondary to abdominal compartment syndrome, and she was placed on maximum respiratory support. Despite all interventions, the patient arrested.

Discussion:

We report a VIAHS ADA2 deficiency diagnosed child with atypical clinical features at disease onset. The clinical description of this girl highlights the variable phenotype associated with ADA2 deficiency due to CECR1 mutations [8]. ADA2 deficiency was first described in two major articles, with fever, visceral and cutaneous lesions compatible with polyarteritis nodosa, and peripheral and central nervous system involvement [8-9]. While the patient in this report eventually demonstrated a comparable spectrum of disease features, she initially presented with a perianal abscess and persistent fever.

ADA2 deficiency should be considered as a differential diagnosis of enlarging cutaneous abscess with no evidence of wound healing in the setting of leukopenia and neutropenia. Our patient exhibited neither hypogammaglobulinemia nor biological markers of autoimmunity (ANA/lupus anticoagulant) nor recurrent infections, even though there was B cell lymphopenia in accordance with the proposed hypothesis that ADA2 deficiency may lead to a defect in memory B cells [4]. Various clinical manifestations of ADA2 deficiency (VAIHS, OMIM#615688) include vasculopathy, skin manifestations, neuropathy, immunodeficiency, and hematology.

Our patient showed a splicing variant c.882-2A>G in ADA2 gene. ADA2 (Adenosine Deaminase 2, OMIM#607575) gene encodes a member of a subfamily of the adenosine deaminase protein family that catalyzes the deamination of adenosine and 2-prime-deoxyadenosine to inosine and deoxyinosine, respectively, and regulates levels of adenosine signaling, cell proliferation and differentiation. Diseases associated

with ADA2 include Sneddon syndrome (SNDNS, OMIM#182410), vasculitis, auto-inflammation, immunodeficiency and hematologic defects syndrome (VAIHS, OMIM#615688), Kaposi sarcoma susceptibility, and Diamond-Blackfan anemia 1. The variant c.882-2A>G (ADA2, NM_001282225.2) is reported in ClinVar and Varsome databases as pathogenic for polyarteritis nodosa or VAIHS and has been previously described to resemble ALPS (autoimmune lymphoproliferative syndrome) like phenotype by Alsutlan et al. 2018 (PMID 29271561) [10-11]. There is no precise genotype-phenotype correlation in the reported ADA2 mutations and further studies are needed to evaluate the effects of this mutation on RNA splicing, stability, and translation. Variability in disease severity has been reported even among patients with the same mutation, as previously reported in individuals with homozygous p.Arg169Gln mutation, indicating potential genetic, epigenetic, and environmental factors in determining the severity of the phenotype [2-3, 6].

The use of steroids, Anakinra, Infliximab, and G-CSF was not effective in this condition. Studies have exhibited benefit from the use of anti-TNF agents such as Entracept and Adalimumab, and Thalidomide resulting in complete remission [5]. In addition, the use of fresh frozen plasma (FFP), considered a crucial therapy in DADA2, was also not beneficial, possibly due to the short half-life of ADA2 [9]. Hematopoietic stem cell transplantation (HSCT) with its potential advantages in the cure of the disease and avoidance of long-term cost and toxicity of lifelong anti-TNF therapy [7,11-12] was an option, and HLA typing was done on both parents. However, the current case did not receive HSCT due to complications. HSCT was reported to treat DADA2 effectively [12].

In summary, the classic DADA2 phenotype includes vasculitis, stroke, livedo reticularis, hepatosplenomegaly, hypogammaglobulinemia, and cytopenia and there is high phenotypic variability in DADA2 [10]. Our patient had cutaneous vasculitis and leukopenia, and neutropenia without evidence of lacunar strokes, organomegaly, and dysregulation of immune response rendering diagnosis more challenging. Thus, screening for DADA2 should be considered in the differential diagnosis in children presenting with persistent fever, cytopenia, and non-healing cutaneous lesions. This report renders that marked phenotypic variability can occur, and screening for families should be initiated in those with evidence of ADA2 mutation. Efforts to collect new cases may allow us to close potential diagnostic gaps, straddling the borders of autoinflammation and immunological deficiency [13]. Importantly, although the pathological basis of this severe disease remains unclear, highly promising therapeutic strategies have already emerged.

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Conflict of Interest:

The authors have no conflict-of-interest disclosure.

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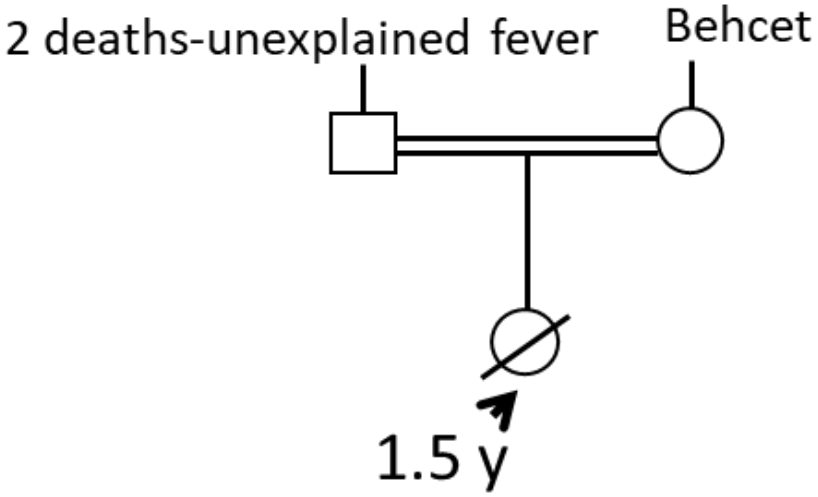
Figure Legend:

Figure 1. A) Family pedigree of the only child (affected) from consanguineous parents with a strong paternal and maternal family history. B) ADA2 gene with some known mutations and splicing mutation (solid boxed) identified in the case.

Figure 1.

A)



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