**Table 1: Clinical characteristic, Genotype, and treatment outcome for Saudi patients with DADA2**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | A1 | A2 | B1 T1 | B2 T2 | B3 | B4 | B5 | C |
| **Current age(year)/Gender** | 17/M | 15/M | 14/F | 14/F | 20/F | 26/F | 11/M | 4/F |
| **Age (year) at onset/diagnosis** | 5/10 | 4.8/9 | Neonate/10 | Neonate/10 | 6/17 | 24/25 | 4/9 | 0.9/3 |
| **Family history** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| **Initial presentation** | HL IIIB | HL IIIA | Inguinal lymphadenopathy | Inguinal lymphadenopathy | HL IIIB | Skin rash, leukopenia | Mouth ulcer  leukopenia | Fever, aphthous ulcer, lymphadenopathy, organomegaly, bruises, pancytopenia |
| **Clinical features/spectrum** |  |  |  |  |  |  |  |  |
| Auto-inflammatory features | Hepatosplenomegaly | Hepatosplenomegaly | Splenomegaly | Splenomegaly | None | None | hepatosplenomegaly | Recurrent fever, transaminases Hepatosplenomegaly |
| Vasculopathy | No | No | Skin rash | Ischemic Stroke, skin rash | No | Skin rash | Ischemic stroke | Ischemic Stroke |
| Immune dysregulation | Hypogammaglobinemi, Recurrent infection (CMV retinitis, mycobacterium riyadhense) | hypogammaglobinemia | Lymphadenopathy, splenomegaly,**hypogammglobinemia** | Lymphadenopathy, Splenomegaly, hypogammglobinemia | No | No | No | Recurrent infection, BCGitis, (latent TB) lymphadenopathy, |
| Musculoskeletal features | No | No | No | No | No | No | Myalgia | No |
| Lab CBC | Anemia (PRCA), lymphopenia, neutropenia,thrombcytopenia, | Lymphopenia, neutropenia | Lymphopenia, neutropenia | Lymphopenia, neutropenia | Neutropenia | Neutropenia, lymphopenia | Neutropenia  lymphopenia | Neutropenia, lymphopenia, anemia, thrombocytopenia |
| ESR/CRP | N/N | N/N | N/N | N/N | N/N | N/N | N/N | Both elevated |
| Igs level | Low Ig A and Ig G | Low IgA, IgG, and IgM | Low Ig A and M, Normal IgG | Low IgM, Low IgG | N | N | N | N |
| Autoantibodies/ANCA | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Renal/Liver testing | N/N | N/N | N/N | N/N | N/N | N/N | N/N | N/transaminases |
| Brain MRI | N | N | N | Ischemic infarct | ND | ND | Ischemic stroke | Ischemic stroke |
| Abdominal ultrasound | Hepatosplenomegaly | Hepatosplenomegaly | Splenomegaly | splenomegaly | N | N | hepatosplenomegaly | hepatosplenomegaly |
| ADA2 enzyme assay (24.9 – 285 mU/g) | 0.0 | 0.0 | 0.0 | 0.0 | 26 | ND | ND | ND |
| ADA2 genetic testing | Homozygous c.1447\_1451del | Homozygous c.1447\_1451del | Homozygous c.882-2A:G | Homozygous c.882-2A:G | Heterozygous c.882-2A:G | Homozygous c.882-2A>G | Homozygous c.882-2A>G | Compound heterozygousada2 c.389\_407del p.(Tyr130Serfs\*48) and c.505C>T p.(Arg169Trp) |
| Additional features | Growth retardation | None | Required growth hormone for Growth retardation | Required growth hormone for Growth retardation | None | Aphthous ulcer | Aphthous ulcer | Aphthous ulcer |
| **Previous Treatment** | HL treatment, Steroid, Anti-TNF, G-CSF | HL treatment | IVIG | IVIG | HL treatment | Anti-TNF | Anti-TNF | Blood products, IVIG |
| **Current Treatment** | Splenectomy, cyclosporine, IVIG | None | Anti-TNF | Anti-TNF | none | Anti-TNF | Anti-TNF | Anti-TNF, IVIG |
| **Outcome** | Stable | Stable | Stable | Stable | stable | Stable | Stable | Improved and off blood products |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | D | E1 | E2 | F | G | H | I | J |
| **Current age (year)/Gender** | 5/M | 6/M | Died at 1.5/F | 8/F | 7/F | Died at 1.8/F | 8/F | 9.5/M |
| **Age at onset/diagnosis** | 1.5/4.8 | 3/3.3 | Neonate/after death | 1.5/5 | 5/5.4 | 1.4/1.6 | 5.5/6 | 0.4/9 |
| **Family history** | No | Yes | Yes | No | No | No | No | No |
| **Initial presentation** | Bruises, thrombocytopenia, hemolytic anemia, neutropenia, hepatosplenomegaly | Fever, weight loss, lymphadenopathy, hepatosplenomegaly | PRCA, alloimmunization, hepatosplenomegaly | Fever, thrombocytopenia, neutropenia, lymphadenopathy (ALPS like presentation) | Fever, neutropenia, sever infection | Fever, perianal abscess and fistula | Abdominal pain, hematemesis, nephropathy, hypertension | Oral ulcer, arthralgia, myalgia |
| **Clinical features/spectrum** |  |  |  |  |  |  |  |  |
| Auto-inflammatory features | Hepatosplenomegaly | Recurrent fever, Hepatosplenomegaly | Hepatosplenomegaly, transaminases | Recurrent fever, hepatosplenomegaly | Recurrent fever, Hepatosplenomegaly | Recurrent fever | Recurrent fever | No |
| Vasculopathy | Stroke, CNC bleed | No | Ischemic stroke, fulminant hepatitis | Skin rash | Abdominal pain | No | Cutaneous PAN, digital necrosis, optic neuritis and atrophy, bowel perforation required ileostomy, mucosal infarction and mural vasculitis from jejeneal biopsy | Stroke with Lower limb weakness |
| Immune dysregulation | Low Ig A | Lymphadenopathy, recurrent infection (CMV viremia) | No | Lymphadenopathy, | Typhilitis, required colostomy, recurrent UTI, urogenital fistula | Recurrent infection (pseudomonas and candida) | Recurrent infection, lymphadenopathy | Low IgM,  IgA IgG N |
| Musculoskeletal features | No | No | No | No | No | No | No | Arthralgia, myalgia |
| Lab CBC | Anemia, lymphopenia, neutropenia, thrombocytopenia | Neutropenia, anemia | Anemia (PRCA) | Neutropenia, thrombocytopenia, lymphopenia | Neutropenia, thrombocytopenia | Neutropenia, lymphopenia | N | Neutropenia, lymphopenia |
| ESR/CRP | N/N | Elevated/N | N/N | Elevated/ND | N/N | Elevated/elevate | Elevated/elevated | N/N |
| Igs | Low Ig A, Ig G, and Ig M | N | N | N | N | Low Ig A, Ig M, and Ig G | N | Low Ig M,  Ig A and G are N |
| ANCA | Negative | Negative | Negative | Negative | ND | Negative | Negative | Negative/negative |
| Renal/Liver testing | N/N | N/N | N/transaminases | N/N | N/N | N/N | Proteinuria/N | N/N |
| Brain MRI | Ischemic and hemorrhagic stroke | ND | Ischemic stroke | Normal | Normal | ND | Leptomeningeal nodular enhancement | Ischemic infarct |
| Abdominal ultrasound | Hepatosplenomegaly | Hepatosplenomegaly | Hepatosplenomegaly | Hepatosplenomegaly, lymphadenopathy | Hepatosplenomegaly | N | N | N |
| ADA2 enzyme assay (24.9 – 285 mU/g) | ND | ND | ND | 0.9 | ND | ND | ND | ND |
| ADA2 genetic testing | Homozygous c.1447\_1451 del p(Ser483Profs Ter5) | Homozygous c.1379T>A. p. Met460Lys Exon 9. Chr 22 | Homozygous c.1379T>A. p. Met460Lys Exon 9. Chr 22 | Homozygous  ADA2.c.882-2A>G | Homozygous c.1447\_1451del p.(Ser483Profs\*5) | Homozygous c.882-2A:G | Homozygous c.139G>C, p.G47R | Homozygous c.144dup p.(Arg49Alafs\*13) |
| Additional features | None | None | None | None | None | None | Growth retardation, lower limb weakness resemble transverse myelitis | Aphthous ulcer,  Patient from Sudan |
| **Previous Treatment** | Corticosteroid, rituximab, Eltrompobag, G-CSF, IVIG | - | Corticosteroid dependent. MMF | Anti-TNF, G-CSF | G-CSF | Corticosteroid, IVIG, anti-TNF | Corticosteroid, IVIG | Corticosteroid |
| **Current Treatment** | Anti-TNF, cyclosporine | Anti-TNF, G-CSF | - | HSCT (MSD) | G-CSF | **-** | Anti-TNF | Anti-TNF |
| **Outcome** | Off blood products support | Improved hepatosplenomegaly, only neutropenia fever persistent | Died at 18 months old with fulminant hepatitis and MOF before the discovery of DADA2 | Cured | Stable | Died of septic shock 2 months after diagnosis | Stable on Anti-TNF | Both clinical and lab improvement |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | K | L | M | N1 | N2 |  |  |  |
| **Current age/Gender\*** | 6/F | 12/M | Died at 5/F | 14 /F | 8/ M |  |  |  |
| **Age at onset/diagnosis** | 5/5.4 | 3/ 10 | 0.2/after death | 3/4 | 1/ 1.3 |  |  |  |
| **Family history** | No | No | No | Yes | Yes |  |  |  |
| **Initial presentation** | Anemia | HL III A | Anemia, hepatosplenomegaly | Anemia | Anemia |  |  |  |
| **Clinical features/spectrum** |  |  |  |  |  |  |  |  |
| Auto-inflammatory features | None | Recurrent fever | Hepatosplenomegaly | None | None |  |  |  |
| Vasculopathy | No | **Not done** | No | No | No |  |  |  |
| Immune dysregulation | No | Recurrent infection | No | Recurrent furunculosis | Recurrent chest infection |  |  |  |
| Musculoskeletal features | Maylagia | Mayalgia | No | No | No |  |  |  |
| Lab CBC | Anemia (PRCA) | Neutropenia | Neutropenia, anemia (PRCA) | Anemia (PRCA), lymphopenia | Anemia (PRCA)  lymphopenia |  |  |  |
| ESR/CRP | ND/Normal | Elevated/Normal | Normal/Normal | ND/ND | N/N |  |  |  |
| Igs | Low ig A, Normal Ig G and M | N | Low Ig G, low Ig M | Low Ig A, Ig M, and Ig G | Low IgA, Ig M, and Ig G |  |  |  |
| ANCA | Negative/ND | Negative/ND | Negative/ND | Not done | Not done |  |  |  |
| Renal/Liver testing | N/N | N/N | N/N | N/N | N/N |  |  |  |
| Brain MRI | N | ND | ND | N | N |  |  |  |
| Abdominal ultrasound | N | N | Hepatosplenomegaly | N | N |  |  |  |
| ADA2 enzyme assay (24.9 – 285 mU/g) | ND | ND | ND | Normal | Normal |  |  |  |
| ADA2 genetic testing | Homozygous c.714\_738dup, p. (Ala247Glnfs\*16) | Homozygous c.1447\_1451del, p. (Ser483Profs\*5) | Homozygous c.1447\_1451del p(Ser483Prof\*5) | Homozygous c1447\_1451del P(ser483Profs\*5) | Homozygous c1447\_1451del P(ser483Profs\*5) |  |  |  |
| Additional features | None | Apthous ulcer | None | Growth retardation | Growth retardation |  |  |  |
| **Previous Treatment** | Corticosteroids, IVIG | HLH treatment | Corticosteroid and chronic blood transfusion | Corticosteroids | Corticosteroids |  |  |  |
| **Current Treatment** | Chronic blood transfusion | G-CSF | - | Chronic blood transfusion | Chronic blood transfusion |  |  |  |
| **Outcome** | Stable on blood transfusion | Stable on G-CSF | No response to steroid. Died with septic MOF | Waiting for suitable HSCT donor | Waiting for suitable HSCT donor |  |  |  |

T1: twin 1. T2 : twin 2. M: male. F: female. Age in year. HL: Hodgkin lymphoma. PRCA: pure red cell aplasia. CBC: complete blood count. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. N: normal. Igs: immunoglobulins. ANCA: antineutrophil cytoplasmic antibodies. MRI: magnetic resonance imaging. ND: not done. IVIG: intravenous immunoglobulin. G-CSF: granulocyte-colony stimulating factor. MMF: mycophenolate mofetil. MOF: multi-organ failure.