

Different Phenotypes of a New Mutation: Two Siblings with ADA-2 Deficiency Presenting with Anemia and Neutropenia (Case Reports and Literature Review)

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ABSTRACT

Deficiency of adenosine deaminase 2 (DADA2) is a childhood-onset disease known with pleiotropic clinical manifestations due to a monogenic form of systemic vasculopathy. Although the clinical spectrum of DADA2, linked to biallelic mutations in the ADA2 gene, has significantly expanded since 2014, approximately 200 cases have been reported thus far. In this report, two siblings are presented to draw attention to an unreported mutation of DADA2 and different phenotypic features of the same missense type homozygous mutation, p.Ser50Leu (c.149C>T). Next-generation sequencing demonstrated an autosomal recessive inherited missense type p.Ser50Leu (c.149C>T) variant homozygous mutation in the ADA-2 gene. The index patient is a 10-year-old Iraqi citizen boy who was referred to us with a complaint of anemia. The patient still needed blood transfusions after 2 hematopoietic stem cell transplantations. His older brother was an 11-year-old boy who presented to the emergency with a history of recurrent lung infections since 7 years of age. Considering the genotype-phenotype relationship from literature data, although vasculitis and low ADA2 activity are defined in cases with missense mutations, immuno-hematological manifestations are remarkable in our patients rather than vasculitic manifestations. While bone marrow failure findings e.g., anemia, neutropenia, etc. are reported to be seen in the 5th and 6th decades of life, those were predominant clinical features in our patients despite their younger age. DADA2 should also be kept in mind in cases of otherwise unexplained cytopenia, especially when associated with panhypogammaglobulinaemia and bone marrow hypocellularity, irrespective of the age of the patient at presentation.

Keywords: Deficiency of adenosine deaminase 2, anemia, neutropenia, livedo racemosa, hypogammaglobulinemia

INTRODUCTION

The adenosine deaminase 2 (ADA2) enzyme is highly expressed in myeloid cells and it is thought to play a role in the differentiation of macrophages. It may have a growth factor activity as well. Deficiency of ADA2 (DADA2) is supposed to be linked to an imbalance in the differentiation of monocytes towards proinflammatory M1 macrophages (1-4). This might be one of the underlying causes of the autoinflammatory process and manifestations of the disease. Also, ADA2 is confused with ADA / ADA1 as an enzyme, but DADA2 patients do not accumulate deoxy-

adenosine nucleotides because of their protected deaminase activity (1,5).

Deficiency of ADA2 is a childhood-onset disease with pleiotropic clinical manifestations due to a monogenic form of systemic vasculopathy. The clinical phenotype of DADA2 has expanded significantly since it was described firstly in 2014 (3). Pleiotropic clinical manifestations include immuno-hematological, systemic autoinflammatory, as well as musculoskeletal system features (1-6). It is linked to biallelic mutations in the ADA2 (previously CECR1: Cat eye syndrome chromosome region, candi-

date 1) gene (6). Twenty-four percent of DADA2 cases are reported before 1 year of age and 77% before the age of ten (7). Currently, approximately 200 cases have been reported worldwide so far (2). Its prevalence is thought to be 4/100.000 people (2).

Here, we aim to draw attention to an unreported mutation of DADA2 as well as two different phenotypic features of this same mutation by presenting 2 sibling patients diagnosed during their follow-up.

CASE PRESENTATIONS

Case 1

Our index patient was a 10-year-old Iraqi citizen boy who was referred to us with a complaint of anemia. He was previously diagnosed with Diamond Blackfan Anemia (DBA) at an external center and received packaged red blood cells every 2-3 weeks beginning from the postnatal 27th day. He was born with normal spontaneous vaginal delivery and had a history of prolonged jaundice. He received allogeneic hematopoietic stem cell transplantation (HSCT) from his mother in 2013 (6 years old) and 2014 (7 years old); however, his need for blood transfusions continued. His parents were Iraqi citizens and first-degree cousins (Figure 1).

His physical examination revealed 24 kg of body weight (3rd percentile), pale skin on inspection, flattened nasal root, and an atypical facial appearance. On auscultation, there were bilateral sibilant rales and coarse rhonchi in the lungs, and the expiration was prolonged. On palpation, 3 cm hepatomegaly and 4 cm splenomegaly were detected. The rest of the physical examination was normal.

The fact that the patient still needed blood transfusions after 2 HSCTs has been a warning for us to reconsider the diagnostic process. The routine biochemical evaluations showed elevated AST, ALT, and LDH levels. Although

a liver biopsy was not performed, the hepatomegaly and splenomegaly were thought to be related to systemic auto-inflammatory manifestations of the disease. Serological evaluations showed panhypogammaglobulinemia and normal complement C3 and C4 levels. Isohemagglutinin titers (anti-A and anti-B titers) were low. Anti-HBs titer (399 IU/mL) was positive. Anti-dsDNA and ANA tests were negative. Flow cytometric analysis of peripheral blood mononuclear cells showed normal T, B, and NK cell percentages, according to his age (Table I-III).

Latest hematological evaluations suggested complete bone marrow failure consisting of leukopenia, anemia, and thrombocytopenia (Table I). Bone marrow aspiration and biopsy showed hypocellularity, reduced megakaryocytes, grade 1 reticulin fibers, very large iron clusters, and iron detected in the extracellular area. The myeloid/erythroid ratio was 9,4. The panel for paroxysmal nocturnal hemoglobinuria was normal. Gene analysis for DBA, DBA-ribosomal protein S (RPS19), and alpha-/beta-thalassemia mutations were negative. Next-generation sequencing (NGS) demonstrated an autosomal recessive

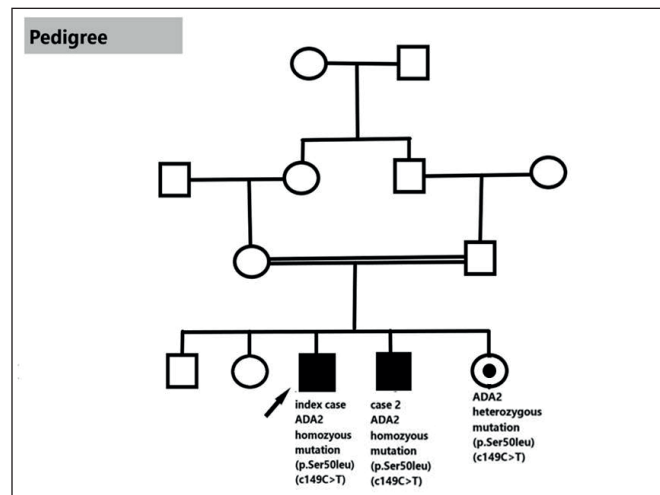


Figure 1. The pedigree of our patient.

Table I: Hematological evaluations of Case 1 (C1) and Case 2 (C2).

Data	WBC/ μ L	LYM (%)	NEU (%)	MONO (%)	EOS (%)	PLT	HGB (g/dl)	MCV (fl)	Ferritin (ng/ml)	Reticulocyte (%)
Highest C1	6.930	1.520 (22)	4.910 (70.9)	249 (3.5)	250 (3.5)	142.000	11.4	85.5	18.288	0.211
Lowest C1	2.490	640 (25.8)	1680 (67.2)	100 (4)	(3) 75	95.400	5.5	74.1	1.031	0.11
Highest C2	13.900	12.800 (92)	19 (0.138)	695 (5)	(3) 417	390.000	12	80.8	13.900	1.77
Lowest C2	1.810	1.720 (95.1)	3 (0.158)	(2) 36	(3) 54	149.000	7.5	72.5	1.810	1.74

C: Highest / lowest values for cases, **WBC:** White blood cell, **LYM:** Lymphocyte, **NEU:** Neutrophil, **Mono:** Monocyte, **EOS:** Eosinophils, **PLT:** Platelet, **HGB:** Hemoglobin.

Table II: Immunological evaluations of Case 1 and Case 2.

Cases	IgG	IgA	IgM	Ig E	IgG1	IgG2	IgG3	IgG4	CD3 (%)	CD4 (%)	CD8 (%)	CD19 (%)	CD56 (%)
Case 1	536	35	<18	<17.2	ND*	ND*	ND*	ND*	65.2	39	26	19.3	15
Case 2	1,750	257	101	<16.9	1,300	150	127	111	94.4	25.4	62.2	0.9	0.1

ND*: Not done due to low IgG level, **Ig**: Immunoglobulin, **IgG1-4**: Immunoglobulin G subgroups, **CD**: Cluster differentiation. The units of all immunoglobulin levels, except IgE, are mg/dl. The unit of IgE is expressed as IU/ml

Table III: Serological evaluations of Case 1 and Case 2.

Cases	Anti-A	Anti-B	C3 g/L	C4 g/L	Anti-HAV	Anti-HBs	Anti-Rubella	ANA	Anti-dsDNA	RF
Case 1	Negative*	Negative*	1.33	0.29	1.02	399 IU/ml	ND	Negative*	Negative*	ND
Case 2	>1:8	>1:8	1.40	0.27	9.73	ND	6.9	Negative*	Negative*	Negative*

*: Absent, **Anti-A/B**: Isohemagglutinin titers, **C3/4**: Complement levels, **Anti-HBs**: Hepatitis B surface antibody, **Anti-dsDNA**: Anti-double-stranded DNA, **ANA**: Antinuclear antibody, **ND**: Not done, **Anti-HAV**: IgG antibody against hepatitis A virus vaccination, **Anti- Rubella**: IgG antibody against Rubella virus vaccination. The units of Anti-HBs are IU/ml. The units of anti-HAV and anti-Rubella are expressed as S/Co (Signal cut off).

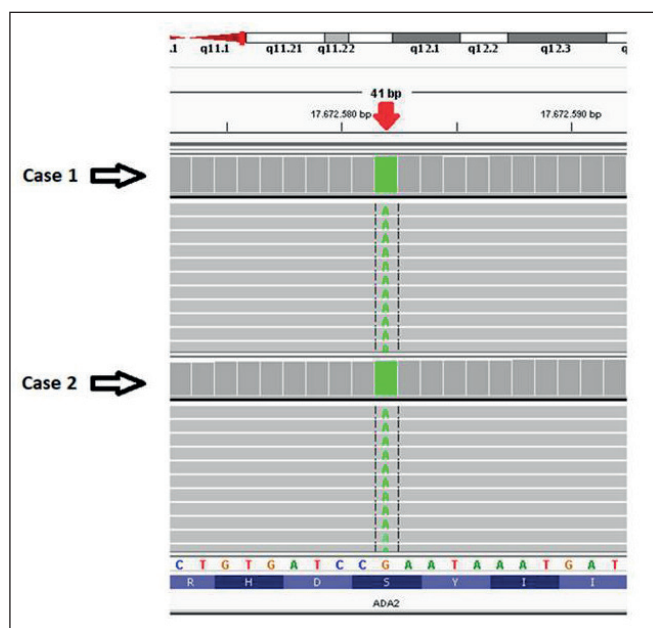


Figure 2. Molecular genetic analysis of the patients. Integrative genomics viewer (IGV) images of the siblings applied 'Hereditary periodic fever syndromes panel (Sophia Genetics SA., Switzerland)' (Consisting of *IL1RN*, *MVK*, *IL10RB*, *IL10RA*, *ADA2*, *TNFRSF11A*, *NOD2*, *MEFV*, *PSMB8*, *TNFRSF1A*, *PSTPIP1*, *NLRP12*, *NLRP7*, *NLRP3*, *LPIN2*, *CARD14*, and *ELANE* genes) on the next-generation sequencing platform (NextSeq 500 system, Illumina, San Diego, California, USA). The variation (chr22-17191692-G-A) is indicated by a red arrow.

inherited missense type p.Ser50Leu (c.149C>T) variant homozygous mutation in the ADA-2 gene (Figure 2). ADA-2 gene mutations were found to be homozygous in

the 3rd and 4th siblings out of 5 siblings in this family, and heterozygous in the 5th sibling who was 4 years old and their mother. The fifth sibling did not have any complaints or pathologic examination findings. This patient is still waiting for his 3rd HSCT (in the preparation phase).

Case 2

His older brother was an 11-year-old boy who presented to the emergency department with complaints of fever up to 39°C, sweating, cough, and mild cyanosis of the mouth and nails. He had a history of recurrent lung infections since 7 years of age. At the age of 9 years, the patient was hospitalized in the pediatric intensive care unit for 4 days and treated with Trimethoprim-Sulfamethoxazole, Meropenem, and Teicoplanin.

During his hospitalization at 11 years of age, his fever was 39.3°C, heart rate: 120/min, respiratory rate: 36/min, blood pressure: 96/56 mmHg, and SpO₂: 90%. The patient's body weight was 25 kg (<3rd percentile) and height was 137 cm (<3rd percentile). Physical examination revealed livedo racemosa on his skin and bilateral cervical microlymphadenopathy, coarse lung sounds on listening, decreased respiratory sounds in the basal part of the left lung, and a 5 cm palpable liver. Thorax CT showed pneumothorax and cystic cavitory areas and fibrotic recessions in the lower anterior lobe of the right lung and postero-lateral lobe of the left lung as well as density increases in mosaic (ground glass) pattern in both lungs indicating bronchiolitis obliterans (Figure 3).

The hemogram showed leukopenia (WBC: 2.680/mm³), neutropenia (neutrophils: 6/mm³), anemia (Hemoglobin: 8.7 g/dl, Hematocrit: 27.8%) and normal platelet counts (390.000/mm³). Hematological evaluations almost always showed chronic neutropenia (Table I). Acute phase reactants such as CRP (334 mg/L; normal range: <5) and Procalcitonin (6,2 µg/L; normal range: <0.5) were elevated. No Mycobacterium tuberculosis complex DNA was detected. The routine biochemical evaluations and the serum immunological evaluations including IgG subtypes, C3, C4, and CH50 levels were normal. Anti-rubella IgG: 6,9 (low-positive), anti-toxoplasma IgG: 2,3 (low-positive), anti-CMV IgG: 241 (low-positive), and anti-HAV IgG: 9,73 (low-positive). ANA and anti-neutrophilic cytoplasmic antibody (ANCA) tests were negative. Flow cytometry showed CD3+ cells: 94.4%, CD4+: 25.4%, CD8+: 62.2%, CD19+ cells: 0.9%, and CD16+/CD56+ cells: 0.1% (B- and NK- cell lymphopenia). Serum IgG level was 1.750 mg/dl, IgA: 391 mg/dl, IgM: 101 mg/dl and IgE: <17,1 IU/ml. IgG subgroup levels were as follows: (IgG1:1,300 [normal range: 787-954] mg/dl, IgG2: 150 [normal range: 195-259] mg/dl, IgG3: 127 [normal range: 47-75] mg/dl, IgG4: 111 [normal range: 34-64] mg/dl). Isohemagglutinin titers (anti-A and anti-B titers) were normal. Anti-dsDNA and ANA were negative (Table I-III). Due to the detection of DADA-2 in his brother's investigation for anemia, next-generation sequencing (NGS) was performed and found to be positive for the same mutation in July 2020. Our patient has undergone HSCT from a matched family donor from

his sister, but he developed chronic graft-versus-host disease (GVHD) with skin and then gastrointestinal system involvement.

DISCUSSION

During the follow-up of these patients, and re-evaluating the current diagnosis and differential diagnoses by recognizing the discrepancies between the diagnosis made in an external center and the clinical condition of the patients, we were able to reach the final diagnosis by combining NGS analysis and other laboratory examinations of the clinical situation (1-3,8). Missense type p.Ser50Leu (c.149C>T) variant was detected as a result of the examinations performed on the index patient diagnosed with DBA and whose transfusion requirement continued despite 2 transplants. This change (variant) was likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria. Considering the genotype-phenotype relationship of DADA2, vasculitis and low ADA2 activity are defined in patients with missense genotype, with at least 3% residual enzymatic activity, in the literature; while earlier bone marrow failure is remarkable with this missense mutation in our patients (1,8). Since two patients from the same family with the same mutation in similar environmental conditions have different phenotypic clinical findings (3), it is important to investigate epigenetic modifications and develop treatment options for this disorder in the future.

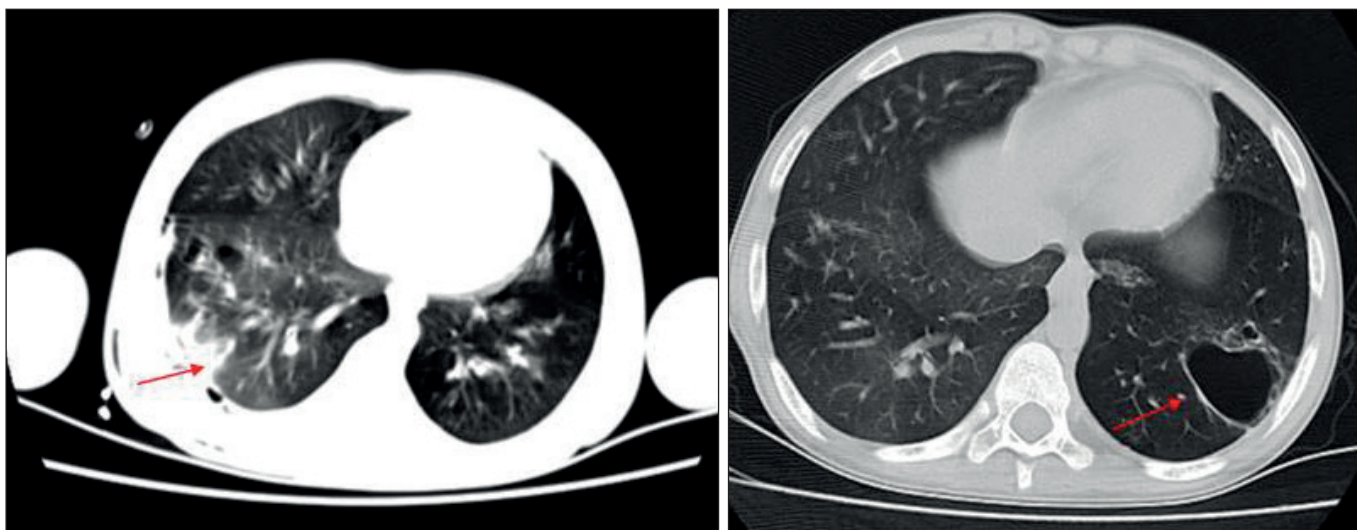


Figure 3. Thorax CT shows pneumothorax, cystic cavitary areas, and fibrotic recessions in the lower anterior lobe of the right lung and postero-lateral lobe of the left lung. There is a mosaic (ground glass) pattern in both lungs indicating bronchiolitis obliterans.

It has initially been recognized as a monogenic vasculitis syndrome that manifests with fevers, vasculitis disorders, and mild immunodeficiency (2,9). It is caused by biallelic hypomorphic/loss of function mutations in the ADA2 gene that encodes the ADA2 protein (5). Anti-neutrophilic cytoplasmic antibody (ANCA) negative vasculopathy begins earlier than 10 years of age and ranges from livedo racemosa / reticularis to early onset polyarteritis nodosa (PAN) or nonspecific eruptions on the skin and life-threatening ischemic and/or hemorrhagic stroke (1,7). Vasculitis and inflammation can affect many organs, explaining the intestinal, hepatological, and renal manifestations (9). Other than simple livedo racemosa in case 2, there was no other symptoms or signs related to vasculopathy/vasculitis in either sibling.

Immuno-hematological manifestations include most commonly hypogammaglobulinemia [low immunoglobulin G, M, and A levels: common variable immunodeficiency (CVID)-like picture], immunodeficiency such as low vaccine response, and lymphoproliferative diseases including lymphadenopathy, pure red cell aplasia, pancytopenia, lymphopenia, immune thrombocytopenia, and neutropenia (1,10-12). The most severe manifestations include marrow aplasia, pure red cell aplasia, and neutropenia (1-3). Immuno-hematological manifestations e.g., anemia, neutropenia, hypogammaglobulinemia, and B-/NK- cell lymphopenia are more prominent in our sibling patients. Anemia in Case 1, but neutropenia in Case 2 are much more prominent features of the same mutation of the ADA2 gene. Although bone marrow failure has been reported to be seen in the 5th and 6th decades of life in the literature, it was a predominant clinical feature in case 1 despite his younger age. Concordantly, Lee et al. identified 15 DADA2 patients presenting with pure red cell aplasia (n=5) or bone marrow failure (n=10) syndrome (8). Most patients did not exhibit features of vasculitis, similar to our index patient (8). Özen et al. from Turkey reported 9/24 DADA2 patients with DBA-like features and 1 patient with immunodeficiency such as in our case 1 (13). Similar to the literature, chronic neutropenia was the major clinical finding observed due to DADA2 in our case 2 and mild-moderate anemia was associated with neutropenia. Neutropenia was sometimes associated with bone marrow failure in case series from the literature. Bone marrow failure might occur at a later age (12,14).

Systemic autoinflammatory manifestations of the disease include intermittent fever, systemic hypertension, and hepato-splenomegaly, and acute phase reac-

tant laboratory findings such as increased CRP, ESR and transaminase (AST, ALT) values during exacerbations are supportive (1,10). In terms of systemic autoinflammatory manifestations of the disease, our patients showed intermittent fever, hepato-splenomegaly and elevated acute phase reactant laboratory findings such as increased CRP, ESR and transaminase values.

Musculoskeletal system features, eye involvement, aphthous ulcers, IBD-like diseases, and hearing loss are variably seen among other clinical findings (1-3). In our patients, there were no signs/symptoms of musculoskeletal system features and others mentioned above.

The first-line treatment consists of TNF inhibitors and is effective in controlling inflammation and in preserving vascular integrity (15,16). Unlike patients with DADA2 with vasculitis, patients with pure red cell aplasia and bone marrow failure have proven largely refractory to TNF inhibitors (8). Since vasculitis/vasculopathy was not our prominent finding, TNF inhibitors were not utilized in either patient.

However, HSCT has been successful in a group of patients presenting with hematological manifestations (4,17,18). Some authors think that HSCT would serve as the first-line curative therapy for the severe form of this disorder (19). A multi-center study has found HSCT to be an effective treatment for DADA2, successfully reversing the refractory cytopenia, as well as the vasculopathy and immunodeficiency (18). Our patient 2 has undergone HSCT from a matched family donor from his sister, but he developed chronic GVHD with skin and then gastrointestinal system involvement. Case 1 is still waiting for his 3rd HSCT (in the preparation phase).

In this report, the diagnosis and then the detection of homozygous and heterozygous mutations of the same gene in the brother and sister of the index patient who had clinical findings of neutropenia and asymptomatic features with the family genetic screening were explained. The current situation highlights the benefit of performing hemato-immunological laboratory and genetic studies together, especially in monogenic diseases, in the diagnosis and follow-up of complicated patients with a wide clinical spectrum (13,20). At the same time, providing genetic counseling to patients with genetic mutations and their families is important for holistic medicine practice.

The different phenotypic (laboratory and clinical) findings of our sibling patients having the same muta-

tion could be summarized as follows: Case 1 started with anemia suggesting DBA, and developed pancytopenia in time, suggesting early bone marrow failure. Bone marrow failure was linked with hypogammaglobulinemia and antibody deficiency against natural (isohemagglutinins) and acquired antigens (vaccines) as well. On the other hand, Case 2 almost always showed neutropenia associated with mild-moderate anemia. Clinical features such as vasculopathy, musculoskeletal system features, eye involvement, aphthous ulcers, IBD-like diseases, and hearing loss were not prominent or detected.

In conclusion; DADA-2 should be suspected in individuals with clinical and laboratory findings of the systemic autoinflammatory disease characterized by vasculitis, hematological abnormalities, and dysregulation of immune system function (1-3,8,13,20). Therefore, DADA2 should be primarily considered in patients with early-onset fevers, rashes, and strokes even in the absence of positive family history (7). DADA2 should also be kept in mind in cases of otherwise unexplained cytopenia, especially when associated with panhypogammaglobulinaemia and bone marrow hypocellularity, irrespective of the age of the patient at presentation (12).

Authorship Contributions

Concept: **Oner Ozdemir**, Design: **Oner Ozdemir**, **Mehmet Fatih Orhan**, **Mustafa Buyukavci**, Data collection or processing: **Mehmet Fatih Orhan**, **Emine Aylin Yilmaz**, **Orhan Gorukmez**, Analysis or Interpretation: **Oner Ozdemir**, **Mehmet Fatih Orhan**, **Mustafa Buyukavci**, **Orhan Gorukmez**, Literature search: **Oner Ozdemir**, **Mehmet Fatih Orhan**, **Mustafa Buyukavci**, **Emine Aylin Yilmaz**, **Orhan Gorukmez**, Writing: **Oner Ozdemir**, **Mustafa Buyukavci**, **Orhan Gorukmez**, Approval: **Oner Ozdemir**, **Mehmet Fatih Orhan**, **Mustafa Buyukavci**, **Emine Aylin Yilmaz**, **Orhan Gorukmez**.

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