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# Deficiency of adenosine deaminase 2 leading to recurrent Hodgkin lymphoma: A case report

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## Abstract

Deficiency of adenosine deaminase 2 is a rare monogenic multi-organ disease of children and less often adults resulting from mutations in the adenosine deaminase 2 gene. We present a case of a 35-year-old Palestinian male with adenosine deaminase 2 deficiency and maturity-onset diabetes of the young type 2. The patient initially presented with complaints of swelling in his neck and night sweats, leading to a diagnosis of Hodgkin lymphoma. Subsequent evaluation revealed a recurrence of Hodgkin lymphoma, along with symptoms of otitis media, upper respiratory tract infection, and a rash around the mouth. Genetic testing confirmed mutations in the adenosine deaminase 2 gene and glucokinase genes, confirming the diagnosis of deficiency of adenosine deaminase 2 and maturity-onset diabetes of the young type 2, respectively. The patient was treated with Intravenous immunoglobulin, antiviral drugs, and oral hypoglycemic drugs, showing improvement in symptoms and laboratory tests. This case highlights the importance of considering rare genetic disorders in patients with unusual or refractory clinical manifestations, and the need for a multidisciplinary approach in such cases.

**Keywords**

DADA2, Hodgkin lymphoma, adult, hepatosplenomegaly, vasculitis

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## Introduction

Deficiency of adenosine deaminase 2 (DADA2) is an uncommon monogenic multi-organ disease of children and less often adults resulting from mutations in the adenosine deaminase 2 gene (ADA2). The prevalence of DADA2 is estimated to be approximately 4:100000.[1] The ADA2 is encoded by chromosome region, candidate1 (CECR1) gene on chromosome 22q11, and its activity based on the deamination of adenosine to inosine. Formerly known as cat eye syndrome CECR1, is characterized by systemic inflammation and vasculopathy that impacts a wide variety of organs. DADA2 was recognized as a form of systemic vasculitis that resembled polyarteritis nodosa.[2,3]

Manifestations of the disease include livedoid rash (reticularis or racemosa), hematological manifestations, recurrent fever, neurological as stroke and polyneuropathy, immunological abnormalities, abdominal involvement, recurrent infections and lymphoproliferation.[4] Rare presentations of DADA2 include hematological manifestations such as Hodgkin lymphoma.[5,6] Such wide-spectrum clinical manifestations require assessment by many sub-specialties, increasing the difficulty of diagnosis and early detection of the disease.[7,8]

Early diagnosis and management are essential, considering the rates of morbidity and mortality. Diagnostic confirmation of DADA2 involves verifying established pathogenic mutations or low enzymatic activity in ADA2.[9]

Early treatment with tumor necrosis factor (TNF) inhibitors shortly after diagnosis leads to substantial enhancements in disease outcomes.[9–11]

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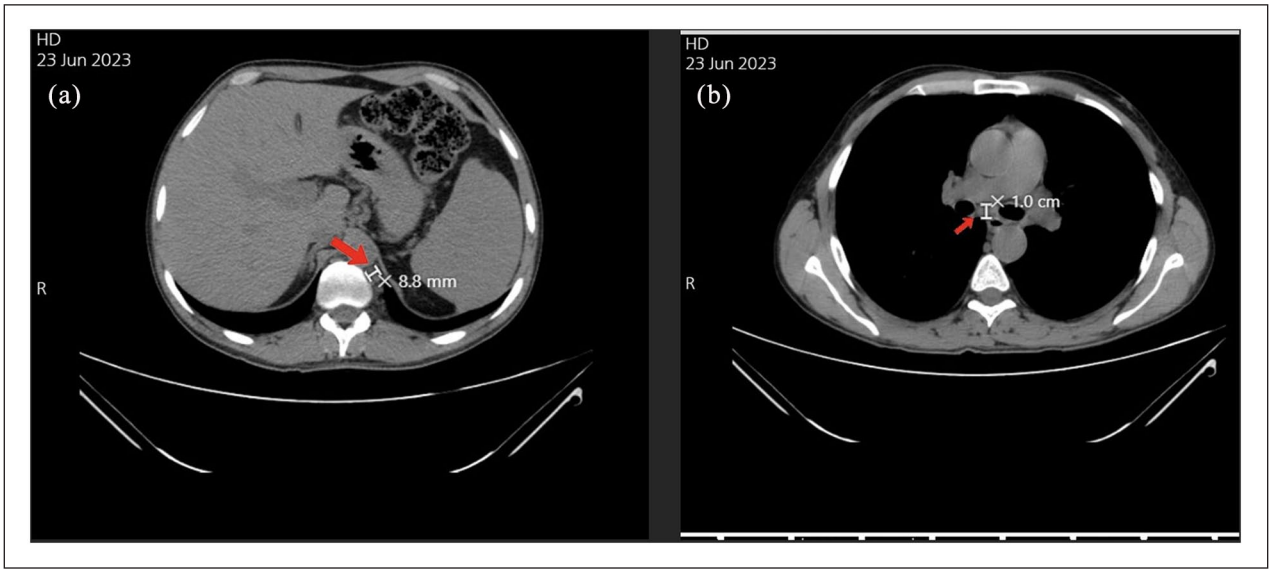


**Figure 1.** (a) Chest CT scan without contrast showed subcrural lymph node enlargement suspect Hodgkin lymphoma. (b) Chest CT scan without contrast showed para-aortic lymph node enlargement suspect Hodgkin lymphoma.

## Case presentation

A 35-year-old Palestinian male patient initially presented in 2012 with complaints of swelling in his neck and night sweats. Imaging studies was not clear then Fine Needle Aspiration was done and the biopsy revealed Hodgkin lymphoma, for which he underwent surgery and received chemotherapy with ABVD Protocol. The mass disappeared, and the patient remained asymptomatic until 2022 when he developed a symptoms of otitis media, URTI and a rash around the mouth, the rash was diagnosed with a herpes virus infection. During a routine follow-up for Hodgkin lymphoma, imaging showed lymph node swelling in the mediastinum (Figure 1(a) and 1(b)). An excision biopsy was planned but delayed due to ongoing inflammation. Subsequent evaluation revealed a recurrence of Hodgkin lymphoma, for which he underwent surgery and started receiving chemotherapy with GDP protocol.

During the fourth dose of chemotherapy, the patient experienced nausea, loss of appetite, vomiting, and continuous fever, hospitalization and intravenous antipyretics were required for symptom management. Before the fifth dose of chemotherapy, the patient developed a continuous fever and a rash around the mouth and nose, consistent with herpes virus infection. Intravenous immunoglobulin (IVIG) was administered, and genetic testing was pursued.

There was no history of headache, weakness, seizures, ataxia, numbness, tingling, memory problems, hearing loss, double vision or vision loss, recurrent fever, abdominal pain, diarrhea and skin discoloration. To characterize and exclude neurological complications, a brain CT scan was performed, revealing normal findings with no evidence of stroke. His past medical history included recurrent herpes zoster infection, gout and chronic hepatitis B. Recently, he diagnosed with maturity-onset diabetes of the young type 2 (MODY2). He had been treated with Glucomet for MODY2, Allopurinol for gout and Tenofovir for hepatitis B.

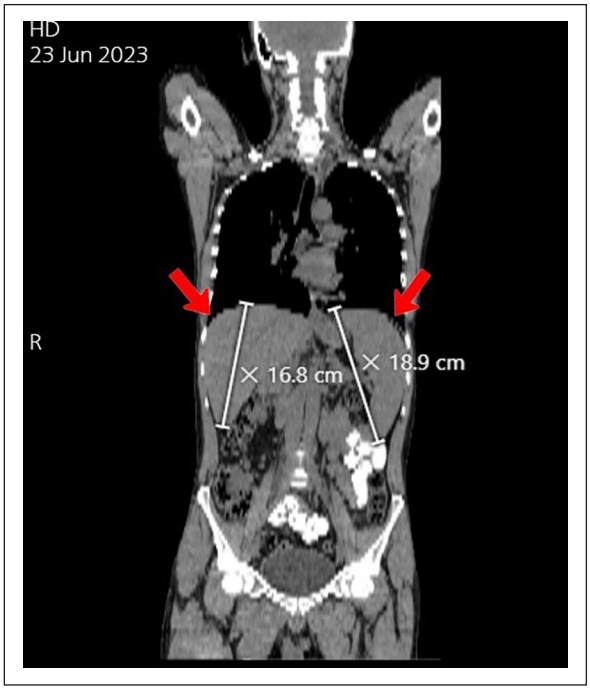


**Figure 2.** Whole body CT scan without contrast showed hepatomegaly approximately 16.8 cm (normal craniocaudal length 10–12.5 cm) and massive splenomegaly approximately 18.9 cm (normal length less than 12 cm).

The patient was febrile (41°C) on physical examination with stable vital signs. On abdominal examination, we observed hepatosplenomegaly showed in (Figure 2).

**Table 1.** Laboratory and genetic data.

| Laboratory data | | | | |
|---|---|---|---|---|
| Test item | | Values before treatment | Values after treatment | Normal values |
| WBC | | 11.3 | 8.3 | 3.9–11 |
| RBC | | 4.04 | 4.15 | 4.3–5.9 million/mm$^3$ |
| HGB | | 9.8 | 11.9 | 13.5–17.5 |
| HCT | | 31.5 | 34.4 | 43.5–53.7 |
| MCV | | 78 | 82.9 | 80–100 |
| MCH | | 24.4 | 31.5 | 27–32 |
| MCHC | | 31.2 | 34.7 | 31–35 |
| IMMUNOGLOBULIN G (IGG) | | 336 | 570 | 600–1640 |
| IMMUNOGLOBULIN A (IGA) | | 94 | 95 | 47–320 |
| IMMUNOGLOBULIN M (IGM) | | 13 | 25 | 50–300 |
| ESR | | 20 | 10 | 0–10 |
| CRP | | 138.09 | 26.30 | <0.3 |
| FASTING BLOOD SUGAR | | 98 | 139 | 70–100 |
| THYROID STIMULATING HORMONE | | 1.00 | 1.2 | 0.55–4.78 |
| RF | | Not done | NEG | Negative <20 |
| Anti-double stranded DNA igA | | Not done | NEG | Negative <10 |
| Anti-double stranded DNA igM | | Not done | NEG | Negative <10 |
| Anti-double stranded DNA igG | | Not done | NEG | Negative <10 |
| ANA SCREEN | | Not done | NEG | |
| C3 | | Not done | 130 | 79.0–152.0 |
| C4 | | Not done | 36.8 | 16.0–38.0 |
| LDH | | 427.9 | 176 | 87–241 |
| BILLIRUBIN, TOTAL | | 0.74 | 0.40 | <1.2 |
| ANA SCREEN | | Not done | NEG | 1:40 |
| Genetic data | | | | |
| Gene | Position | Nucleotide | Zygosity | ACMG Classification |
| ADA2 | 22:17662799 | c.1353G>T | HOM | Likely Pathogenic |
| GCK | 7:44192980 | c.128G>A | HET | Pathogenic |

ADA2: adenosine deaminase 2; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCK: glucokinase; HET: heterozygous; HGB: hemoglobin; HOM: homozygous; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; WBC: white blood cell.

Laboratory tests showed microcytic normochromic anemia (hemoglobin (HB) 9.8 gm/dl, mean corpuscular volume 78.0 FL, mean corpuscular hemoglobin (MCH) 24.4 pg), lymphopenia (lymphocytes 0.6 × 109/L), hypogammaglobulinemia (immunoglobulin M (IgM) 13 mg/dl, immunoglobulin G (IgG) 336 mg/dl), elevated erythrocyte sedimentation rate 20 Mm/h and C-reactive protein 138.09 mg/L. Table 1 demonstrate the difference in the lab values before and after the initiation treatment.

Whole exome sequencing (WES) was prompted by the patient's persistent fever and the absence of a definitive diagnosis despite extensive medical evaluation. Given the complexity of the patient's symptoms, which included recurrent infections and hematologic abnormalities, there was a suspicion of an underlying genetic etiology. The sequencing was performed by MAKASSED ISLAMIC CHARITABLE HOSPITAL following standard protocols. Genetic test showed that the patient is affected with DADA2, also he has MODY2. The Homozygous missense C->A substitution at chr22:17662799 is predicted to result in abnormal protein translation of the ADA2 gene, leading to the amino acid change p.Leu451Phe. Additionally, there is a heterozygous missense C->T substitution at chr7:44192980 is predicted to result in abnormal protein translation of the GCK gene, leading to the amino acid change p.Arg43His. Details of WES are shown in (Table 1).

The patient referred to rheumatology clinic, to follow up disease course, and after researching in the patient's history, it was decided not to give Anti-TNF medication to prevent further decline in patient immunity, and keep on IVIG.

## Discussion

This is a complex and rare case of a patient with Hodgkin lymphoma and DADA2, a genetic disorder that affects the immune system and blood vessels. Hodgkin lymphoma is a rare monoclonal lymphoid neoplasm with high cure rates, typically originating from B-cells.[12] DADA2 represents a recently identified disorder arising from mutation in the ADA2 gene, responsible for producing an enzyme crucial

for controlling adenosine and deoxyadenosine concentrations within the body.[7] DADA2 can cause various symptoms, such as recurrent fever, skin rash, stroke, cytopenia, liver disease, and increased susceptibility to infections.[5,13] The association of DADA2 with lymphoproliferation, such as Hodgkin lymphoma, is rare but has been reported in several cases. The exact mechanism of this link is unclear, but it may involve impaired apoptosis, chronic inflammation, or genetic predisposition.[13]

The patient had several complications and comorbidities, such as herpes virus infection, otitis media, URTI, hepatitis B, and diabetes. Some of these may be related to DADA2, such as herpes virus infection, which is common in patients with immunodeficiency, and diabetes, which may be caused by MODY2, a form of monogenic diabetes that is associated with mutations in the GCK gene, which is also involved in adenosine metabolism. Others may be due to chemotherapy, such as cytopenia and infection, or unrelated, such as gout and hepatitis B.

The mutations identified in our patient, particularly in the catalytic domain of ADA2, have been previously associated with hematological manifestations of DADA2. These mutations can lead to abnormal protein translation, affecting the enzymatic activity of ADA2 and potentially contributing to the hematological abnormalities observed in DADA2 patients. Previous studies have reported similar findings, highlighting the importance of these mutations in the pathogenesis of DADA2.[14,15] Further research is needed to elucidate the exact mechanisms by which these mutations contribute to hematological manifestations and to explore potential targeted therapies for DADA2 patients with hematological complications.

Hodgkin lymphoma treatment varies based on the disease's stage, subtype, and risk factors. ABVD, which consists of vinblastine, doxorubicin, bleomycin, and dacarbazine, is the typical first-line treatment. The patient in this case was treated with ABVD protocol, which is the typical course of treatment for early-stage disease. However, he relapsed after 10 years and was switched to GDP, a different combination of three medications: gemcitabine, dexamethasone, and cisplatin. This is a salvage regimen that is used for patients who fail or are ineligible for autologous stem cell transplantation, which is the preferred option for relapsed or refractory disease.[6]

The treatment for DADA2 is still evolving, the main goal is to prevent or reduce the frequency and severity of strokes, its most serious complication. The current standard involves anti-TNF therapy like etanercept or infliximab to manage inflammation and vascular damage. However, anti-TNF may increase the risk of infection and malignancy, and may not be effective for all patients. Other options include steroids, immunosuppressants, IVIG, and hematopoietic stem cell transplantation, which may have a curative potential for DADA2.[5,13]

In this case, the patient received IVIG before the fifth cycle of GDP, potentially to address a herpes virus infection or bolster the immune system. Notably, IVIG might also offer benefits for DADA2 by modulating immune responses and decreasing autoantibody production. After careful consideration and consultation with a multidisciplinary team, including rheumatologists, immunologists, and hematologists, it was decided not to initiate anti-TNF therapy. This decision was based on the patient's complex medical history, which included a concurrent diagnosis of Hodgkin lymphoma, DADA2, and MODY2, as well as the potential risks associated with anti-TNF therapy, such as an increased risk of infection and malignancy. Additionally, the patient's plasma ADA2 activity was not measured, which could have provided valuable information regarding the potential benefit of anti-TNF therapy. Moreover, the patient exhibited a positive response to IVIG, demonstrating noticeable improvements in both clinical symptoms and relevant laboratory markers.

The decision not to pursue bone marrow transplantation (BMT) for the patient was based on their complex medical history, which included Hodgkin lymphoma, DADA2, and MODY2, as well as comorbidities like chronic hepatitis B, gout, and recurrent infections. Despite a satisfactory response to chemotherapy and other treatments, the multidisciplinary team concluded that the risks associated with BMT outweighed the potential benefits in this case.

The patient's prognosis is uncertain due to concurrent serious conditions, including relapsed Hodgkin lymphoma and DADA2. The survival rate of DADA2 is unknown, as the condition is rare, but it may be influenced by the frequency and severity of strokes, infections, and malignancies.[5,6,13] Managing this complex case requires a multidisciplinary approach, genetic counseling for family members, and psychosocial support to improve the patient's quality of life.

## Conclusion

In conclusion, we report the first case in Palestine of an adult patient present with recurrent Hodgkin lymphoma diagnosed with DADA2. Patients with adult-onset DADA2 usually present with nonspecific signs and symptoms which produce additional challenges for the physician to add DADA2 to the list of differentials. It highlights the importance of considering rare genetic disorders in patients with unusual or refractory clinical manifestations, and the need for multidisciplinary collaboration and genetic counseling in such cases. Further studies are recommended to explore the genotype-phenotype association, clinical presentations, and the advancement of curative treatments for such cases.

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## Author contributions

A.M. and M.Q. contributed to study design and manuscript drafting; A.M., M.Q., J.A., A.W. contributed to data collection, data entry, and data interpretation; S.D., O.A. contributed to drafting and supervision of the manuscript; L.A., L.K. contributed to design of the study, data interpretation, and supervision of the work. All authors have read and approved the final manuscript. Each author has participated sufficiently in the work to take public responsibility for the content.

## Data availability

The article contains all the data that support the study's findings and are readily accessible.

## Declaration of conflicting interests

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## Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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## References

1. Kendall JL and Springer JM. The many faces of a monogenic autoinflammatory disease: adenosine deaminase 2 deficiency. *Curr Rheumatol Rep* 2020; 22: 1–10.
2. Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med* 2014; 370: 911–920.
3. Navon Elkan P, Pierce SB, Segel R, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *N Engl J Med* 2014; 370: 921–931.
4. Maccora I, Maniscalco V, Campani S, et al. A wide spectrum of phenotype of deficiency of deaminase 2 (DADA2): a systematic literature review. *Orphanet J Rare Dis* 2023; 18: 1–14.
5. Alabbas F, Alsharief O, Meyts I, et al. Deficiency of adenosine deaminase 2 (DADA2) presenting as familial hodgkin lymphoma. *Blood* 2018; 132: 5373.
6. Alabbas F, Elyamany G, Alsharif O, et al. Childhood hodgkin lymphoma: think DADA2. *J Clin Immunol* 2019; 39: 26–29.
7. Meyts I and Aksentijevich I. Deficiency of adenosine deaminase 2 (DADA2): updates on the phenotype, genetics, pathogenesis, and treatment. *J Clin Immunol* 2018; 38: 569–578.
8. Hedrich CM, Cavazzana M and Lee PY. Vasculopathy, immunodeficiency, and bone marrow failure: the intriguing syndrome caused by deficiency of adenosine deaminase. *Front Pediatr* 2018; 6: 282.
9. Alharthi A, Alamer GRA, Alqurashi SS, et al. A unique case of deficiency of adenosine deaminase 2 single in a young adult patient. *Cureus* 2023; 15: e33273.
10. Lee PY, Davidson BA, Abraham RS, et al. Evaluation and management of deficiency of adenosine deaminase 2: an international consensus statement. *JAMA Netw Open* 2023; 6: e2315894.
11. Sharma A, Naidu GSRSNK, Sharma V, et al. Deficiency of adenosine deaminase 2 (DADA2) in adults and children: experience from India. *Arthritis Rheumatol* 2021; 73: 276.
12. Kaseb H and Babiker HM. Hodgkin lymphoma. *StatPearls*, https://www.ncbi.nlm.nih.gov/books/NBK499969/ (2023, accessed 16 February 2024).
13. Advani RH, Abramson JS, Dutia MP, Fisher RI and Zelenetz AD. Patient case studies and panel discussion: lymphoma. *J Natl Compr Canc Netw*. 2019;17(11.5):1420–1423. https://jnccn.org/view/journals/jnccn/17/11.5/article-p1420.xml
14. Pilania RK, Banday AZ, Sharma S, et al. Deficiency of human adenosine deaminase type 2—A diagnostic conundrum for the hematologist. *Front Immunol* 2022; 13: 869570.
15. Albalawi R, Hanafy E, Alnafea H, et al. Novel adenosine deaminase 2 (ADA2) mutations associated with hematological manifestations. *J Investig Med High Impact Case Rep* 2021; 9: 23247096211056770.