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Case report
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A Rare Case of Newly Acquired Hemophilia Following Diabetic Ketoacidosis in A Male Patient with IL-2 (Rs2069762) Polymorphism

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ABSTRACT

Background: Diabetes is commonly linked to autoimmune processes, but acquired hemophilia A (AH)—a rare bleeding disorder due to factor VIII (FVIII) inhibitors—remains uncommon, particularly during diabetic ketoacidosis (DKA). Recent studies have suggested a role of IL-2 (rs2069762) polymorphism in FVIII inhibitor development. This study aims to highlight a rare case of newly acquired hemophilia coinciding with DKA and the presence of IL-2 gene polymorphism.
Case Presentation: A 40-year-old male presented with dyspnea, abdominal pain, and signs of DKA. He had a history of drug-induced rash due to sulfasalazine. Initial management with IV fluids and insulin resolved the metabolic crisis. However, on day two, he developed spontaneous bruising and gross hematuria. Laboratory tests revealed a low FVIII inhibitor titer (1.2 BU) and positive insulin antibodies. Genetic testing showed TT homozygous polymorphism of IL-2 (rs2069762), potentially contributing to FVIII inhibitor formation.
Results: The patient was treated with low-dose cyclophosphamide and methylprednisolone, followed by rituximab due to poor initial response. Intensive insulin therapy was also administered. After five weeks, clinical remission of AH was achieved, although the patient remains at risk for relapse due to the IL-2 polymorphism.
Conclusion: This case illustrates a rare interplay between DKA and acquired hemophilia, potentially mediated by IL-2 (rs2069762) polymorphism. Prompt diagnosis and individualized immunosuppressive therapy are essential. The findings support further investigation into genetic predispositions in AH pathogenesis during autoimmune or metabolic stress events like DKA.

Keywords: Diabetes, hemophilia, hemorrhagic, autoimmune, polymorphism, gene.

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BACKGROUND

High blood glucose levels are a defining feature of diabetes mellitus (DM), which is associated with both microvascular and macrovascular consequences (Sugandh *et al.*, 2023). It includes a broad range of disorders with various pathophysiological causes. Certain subtypes may be acquired,

inherited, or of autoimmune origins (Gimenez-Perez *et al.*, 2022). Conversely, acquired hemophilia (AH) A is a very uncommon, poorly understood, and underdiagnosed condition. It frequently presents with a severe, rapid-onset clinical presentation and has a high death rate (Cruz *et al.*, 2021).

Acquired hemophilia A (AHA) is a rare autoimmune disorder characterized by the development of autoantibodies (inhibitors) against coagulation factor VIII, leading to potentially life-threatening spontaneous bleeding in patients without a prior history of bleeding disorders (Collins et al., 2010; Knoebl et al., 2012; Franchini & Lippi, 2008).

The incidence of acquired hemophilia is estimated to be 1.5 per million per year, and although rare, it can present with severe clinical symptoms including intramuscular hematomas, mucosal bleeding, and prolonged activated partial thromboplastin time (aPTT) with a normal prothrombin time (PT) (Huth-Kühne et al., 2009; Kessler, 2015; Tiede et al., 2011).

Diabetic ketoacidosis (DKA), a serious metabolic complication of diabetes mellitus, is known to provoke systemic inflammatory and immune responses, which may contribute to the unmasking or triggering of autoimmune phenomena (Kitabchi et al., 2009; Nyenwe et al., 2015; Umpierrez et al., 2002).

Interleukin-2 (IL-2), a cytokine central to the maintenance of immune homeostasis and regulatory T cell development, has been implicated in the pathogenesis of several autoimmune diseases (Malek, 2008; Gregori et al., 2010; Dorman et al., 2004).

A functional single nucleotide polymorphism (SNP) in the IL-2 gene promoter region (rs2069762, also known as -330T/G) has been associated with altered IL-2 expression and increased susceptibility to autoimmune conditions such as systemic lupus erythematosus, type 1 diabetes mellitus, and rheumatoid arthritis (Tang et al., 2012; Eskdale et al., 1998; Wang et al., 2011). However, to date, no case has reported a potential interaction between IL-2 (rs2069762) polymorphism, diabetic ketoacidosis, and the development of acquired hemophilia.

There are little and dubious data in the literature about the relationship between AH and DM. However, the polymorphism IL-2 (rs2069762) has recently been associated with hemophilia A (Marwanta et al., 2023). In this study, we reported a rare case of newly AH following diabetic ketoacidosis in a diabetic male patient with IL-2 (rs2069762) polymorphism.

In this report, we present a rare case of newly acquired hemophilia following DKA in a male patient with the IL-2 rs2069762 polymorphism, highlighting the potential interplay between metabolic crisis, immune dysregulation, and genetic susceptibility.

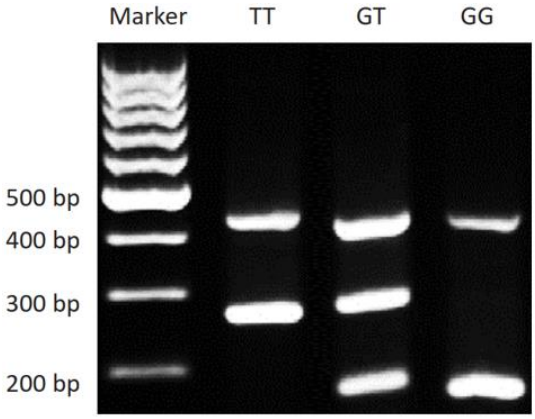
CASE PRESENTATION

A 40-year-old Javanese male with a known medical history of drug-induced rash due to sulfasalazine four months ago presented to emergency department for dyspnea and abdominal pain. He had signs of hypovolemic shock, hyperglycemia (345 mg/dL), ketonemia (6.7 mmol/L), and significant anion gap metabolic acidaemia. However, neither electrolyte imbalance nor signs of infection were detected. We diagnosed him as diabetic ketoacidosis (DKA).

His condition resolved with aggressive intravenous hydration and insulin infusion. However, he showed up with easy bruising and gross haematuria on the second day.

Coagulation studies revealed a prolonged aPTT (74.9s; normal 23–38s) and low FVIII activity (1.9%; normal 50–150%) without significant abnormalities in PT, platelet count, FIX levels or Von Willebrand factor. Prior exposure to blood products was denied. He had low titer of 1.2 Bethesda Units of FVIII inhibitor. Hence, we diagnosed him with newly AH A.

Autoimmune tumor panels and imaging were investigated to determine the potential origins of AH. Antibodies against islet cells and glutamate decarboxylase were negative, whereas those against insulin showed 2.6 IU/L. Single nucleotide polymorphism (SNP) of IL-2 (rs2069762) gene was investigated as it is linked with severe FVIII inhibitor development according to current study. It showed 409 bp and 289 bp indicating TT recessive homozygote as T allele has a role in IL-2 mediated FVIII inhibitor development (Figure 1).



(A)

Primer	Primer sequence 5′ to 3′	Product size
Forward inner (G allele)	TGCTATTCACATGTTCAGTGTAGTTTCAT	179 bp
Reverse inner (T allele)	AAAGTAACTCAGAAAATTTTCTTTGCCC	289 bp
Forward outer	TAGCGTTAAACAGTACCTCAAGCTCAAT	409 bp
Reverse outer	GATGTAGGTGAAATCCCTCTTTGTTACA	

(B)

Genotype	Phenotype (traits)	Band size of the DNA strand		
		Band-1	Band-2	Band-3
GG	Major (dominant) homozygote	179 bp	409 bp	-
TT	Minor (recessive) homozygote	289 bp	409 bp	-
GT	Heterozygote or intermediate	179 bp	289 bp	409 bp

(C)

Figure 1. (A) Electrophoresis arrangement results of T-ARMSPCR for the IL-2 (rs2069762) gene polymorphism. TT is polymorphism type, meanwhile GG and GT is wild type accross population; (B) The primer profile of the IL-2 (rs2069762) gene for T-ARMS-PCR; (C) Genotype, Phenotype (traits) and its product size for each genotype from the T-ARMS-PCR product of IL-2 (rs2069762) gene. IL-2=interleukin-2; rs=restriction site; T-ARMS-PCR=tetra-primer amplification refractory mutation system-polymerase chain reaction.

Less than a day later, the bleeding was stopped by bladder saline lavage. Without requiring a blood transfusion, hemoglobin levels dramatically decreased from an initial value of 14 mg/dL to a minimum of 7.5 g/dL. Because of FVIII inhibitor presence, adequate immunesuppression was initiated. For five weeks, Cyclophosphamide 125 mg/day and slightly increased Methylprednisolone 40 mg/day—0.5 mg/kg/day was administered to prevent additional glycaemic decompensation and because of emergence of FVIII inhibitors during premedication of glucocorticoid regimen (Marwanta *et al.*, 2021). After the initial bleeding episode, with therapy, no further haemorrhage was found despite worsening of the aPTT (81.7 to 119s), residual FVIII activity (<0.6%) and FVIII inhibitor (2.59 BU). Hence, Methylprednisolone (1 mg/kg/day) and weekly rituximab (250 mg) were initiated due to first-line eradication treatment failure. For DM, a 70-unit intensive insulin therapy regimen was given daily.

A 5-week course of methylprednisolone and rituximab resulted in the achievement of disease remission. He was

continued on corticosteroids and tapered over 3 months. Subsequently, four months later, aPTT normalization occurred, and inhibitor levels remained undetectable until this day. The patient is still receiving corticosteroid therapy at this time (methyl-prednisolone 8 mg/day), and there is no history of major bleeding or clinical indication of it, despite he is prone to rebleeding due to his TT genotype of IL-2 (rs2069762) SNP (Marwanta *et al.*, 2021, 2023).

DISCUSSION

Glycaemic markers, which are established in both clinical and laboratory settings, are used to diagnose diabetes mellitus. This illness includes a wide range of disorders with various pathophysiological causes and behaviors. If left untreated, it can result in macrovascular and microvascular problems (Liu *et al.*, 2022). AH occurs owing to an acquired deficit of FVIII secondary to FVIII inhibitor. These antibodies are mainly polyclonal IgG and target more frequently FVIII. Its relationship with various immune-mediated illnesses have been established.

Patients with bleeding diathesis and an isolated prolonged aPTT should be suspected of having AH. Low FVIII activity in combined with a positive FVIII inhibitor, confirms the diagnosis (Sarmiento Doncel *et al.*, 2023).

Treatment consists of stopping and preventing bleeding episodes, eliminating the inhibitor (using immunosuppresnat), and finally diagnosing and treating the underlying condition. High-dose corticosteroids, cyclophosphamide, and/or rituximab are examples of inhibitor eradication techniques that ought to be used as soon as a diagnosis is made (Marwanta *et al.*, 2021). As first-line therapy, the available research supports combination therapy with corticosteroids (prednisolone or methylprednisolone 1 mg/kg/day) and cyclophosphamide (1.5 mg/kg/day). As there are currently no established criteria for patient follow-up, follow-up tactics are primarily empirical and ought to involve routine clinical and laboratory assessments. The prognosis is uncertain (Zanon, 2023).

The data provided raises an unjustified but plausible concern regarding whether the enormous release of pro-inflammatory cytokines (IL-1, -2, -10, and TNF-α) could foster the production of new antibodies and new onset AH. By investigating the SNP (rs2069762) IL-2 gene, we found that this patient possessed TT recessive homozygote as T allele has a role in IL-2 mediated FVIII inhibitor development (Marwanta *et al.*, 2023). Moreover, organ-specific immune-mediated disorders are believed to be linked to Type 1 DM. Nevertheless, pancreatic islet cell damage in type 1 diabetes mellitus is thought to be mediated by cellular immunity (T cells), unlike what is observed in AH (Popoviciu *et al.*, 2023). Finally, it should be noted that while the described bleeding episode was quickly brought under control using non-invasive hemostatic techniques, a cycle of high-dose corticosteroids, cyclophosphamide, and rituximab was necessary to temporarily bring the disease into remission.

AH is a rare and potentially fatal disease. Numerous diseases, including immunological-mediated disorders, medications, hepatitis, and cancers, have been linked to it. Conversely, DM is highly prevalent and typically lacks a clear underlying cause that may be addressed. To our knowledge, this is the first example of AH emerging in the context of a DKA due to the SNP of TT homozygote within (rs2069762) IL-2 gene, and it ought to increase awareness of the potential link between the two conditions and molecular basis.

AUTHORS CONTRIBUTION:

FM conceptualization, methodology, data curation, formal analysis, writing – original draft, and project administration. AGPA investigation, data collection, validation, and writing – review & editing. SM supervision, resources, critical revision of the manuscript, and final approval of the version to be published.

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CONFLICT OF INTEREST

The authors do not have competing interests.

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