

Pathogenic *TET2* Variants and Autoinflammatory Manifestations in Myeloid Hematologic Malignancies: Case Report and Literature Review

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Abstract

Emerging evidence suggests that somatic mutations in genes associated with innate immunity can trigger adult-onset autoinflammatory diseases. Notably, loss-of-function variants in the *TET2* gene have been linked to both hematological malignancies and immune-mediated disorders. A case is presented of a 73-year-old woman with chronic myelomonocytic leukemia who developed severe pericardial effusion secondary to inflammatory serositis, associated with a pathogenic *TET2* variant. Despite initial treatment with corticosteroids and diuretics, her condition worsened, which led to the need to implement treatment with colchicine and anakinra. This regimen led to significant clinical improvement and resolution of the effusion. This case reflects the importance of searching for pathogenic variants in *TET2* in patients with hematological disorders, with the aim of early recognition of inflammatory manifestations associated with this genetic alteration. Treatment with colchicine and anti-interleukin-1 should be considered in these cases, as they are effective and avoid the unnecessary use of other immunosuppressants.

Keywords: Autoinflammation, autoinflammatory diseases, chronic myelomonocytic leukemia, pericardial effusion, *TET2*

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Introduction

The *TET2* gene encodes an enzyme that modulates the renewal of hematopoietic stem cells.¹ Loss-of-function variants in this gene contribute to the development of hematological malignancies, particularly of the myeloid lineage.² Recent studies have highlighted the role of *TET2* in regulating the innate immune response and the pathogenesis of late-onset autoinflammatory diseases.³

There have been reports of patients with myeloid neoplasms presenting with autoinflammatory phenomena in association with loss-of-function mutations in *TET2*, which are associated with an increase in proinflammatory cytokines of the interleukin-1 (IL-1B) pathway.³ Additionally, it has been suggested that variants in this gene increase the risk of atherosclerotic cardiovascular disease and myocardial dysfunction.⁴

The aim of this paper is to present a case of inflammatory serositis in a patient diagnosed with chronic myelomonocytic leukemia (CMML) who had a pathogenic variant in *TET2*. A literature review was conducted to highlight the importance of immune-mediated phenomena associated with this genetic alteration.

Case Presentation

A 73-year-old woman with a medical history of untreated CMML was admitted to the Internal Medicine Department due to acute heart failure. The patient reported progressive dyspnoea following minimal exertion, pleuritic chest pain and cough without expectoration. She also experienced orthopnoea and peripheral edema, but denied having fever, chills, or weight loss. Physical examination revealed the patient was afebrile but tachypnoeic, with marked jugular venous distension and decreased breath sounds at both lung bases.

Initial laboratory tests showed an elevated erythrocyte sedimentation rate (ESR) of 42 mm/h, C-reactive protein (CRP) of 122 mg/L, NT-proBNP of 5293 pg/mL, and a high monocyte count of 21 210/mm³. A chest x-ray revealed cardiomegaly and moderate bilateral pleural effusion. An echocardiogram was performed

showing moderate-to-severe pericardial effusion with incipient evidence of cardiac tamponade, but no hemodynamic instability.

On the third day of hospitalization, the patient's condition worsened with hypotension, tachycardia, and increased respiratory distress. Diuretic therapy was discontinued, and an urgent pericardiocentesis was performed. A contrast-enhanced computed tomography scan revealed chronic spleen enlargement, and pleuropericardial effusion with pericardial enhancement (Figure 1). The pericardial fluid analysis revealed a predominance of granulocytes and abundant monocytes of mature appearance, with no malignant cells. Several bilateral axillary lymph nodes were biopsied using fine-needle aspiration. The histopathological examination ruled out metastasis from solid tumors or lymphoproliferative disorders.

A comprehensive examination ruled out infectious diseases, other malignant causes of pleural effusion, and typical autoimmune diseases. Based on these findings and the signs of congestion, the patient was initially treated with intravenous furosemide, colchicine, and oral corticosteroids. Given the leukocytosis with marked monocytosis due to CMML, treatment with hydroxyurea was initiated after consultation with the Hematology Department.

After a week of corticosteroid and colchicine therapy, the patient's condition remained stable but required ongoing oxygen support, and mild pleuropericardial effusion persisted. Due to consistently elevated acute phase reactants and the exclusion of infectious causes,

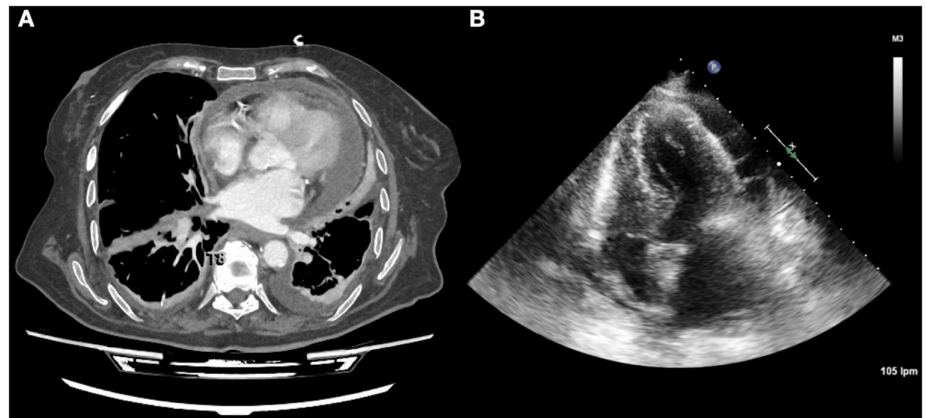


Figure 1. (A) Thoracic CT scan showing a large pericardial effusion, bilateral pleural effusion (more marked on the right side), and areas of atelectasis in the adjacent lung tissue due to compressive effects. (B) Transthoracic echocardiogram in the four-chamber view confirming a fibrinous pericardial effusion, with diastolic collapse of the right atrium indicating tamponade physiology. CT, computed tomography.

treatment with subcutaneous anakinra was initiated.

The introduction of anakinra resulted in rapid and significant clinical improvement. The pleuropericardial effusion resolved, respiratory status improved, and acute phase reactants decreased progressively. Bedside ultrasound was used to monitor both pleural and pericardial effusions, showing complete resolution. Figure 2 illustrates the reduction in CRP, ESR, and monocyte counts following anakinra initiation.

At the time of the patient's discharge, a peripheral blood study of pathogenic variants in different genes related to chronic myelomonocytic leukemia was requested, which identified mutations in *KRAS*, *NRAS*, and *TET2*. The variants

identified in *TET2* were p.Q243* (c.727C>T) and lap.E432fs (c.1294_1295delGA), which were associated with a loss of *TET2* function.

During the outpatient follow-up, the patient remained clinically stable with subcutaneous anakinra, with no evidence of recurrence of serositis. Inflammatory markers and NT-proBNP normalized after 3 months and remained asymptomatic without new inflammatory flare-ups.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Discussion

Autoinflammatory diseases are caused by immune dysregulation due to variants in

Main Points

- Pathogenic variants in *TET2* in patients with myeloid hematological malignancies are associated with systemic inflammation and autoinflammatory manifestations.
- This case illustrates the effectiveness of anti-interleukin-1 in combination with colchicine in controlling inflammatory phenomena associated with *TET2*.
- Further studies are needed to identify the pathogenic mechanisms of *TET2*-associated autoinflammatory manifestations, with the aim of identifying new therapeutic targets.
- It is important to understand the clinical implications of pathogenic variants in *TET2*, as this could explain inflammatory and cardiovascular manifestations.

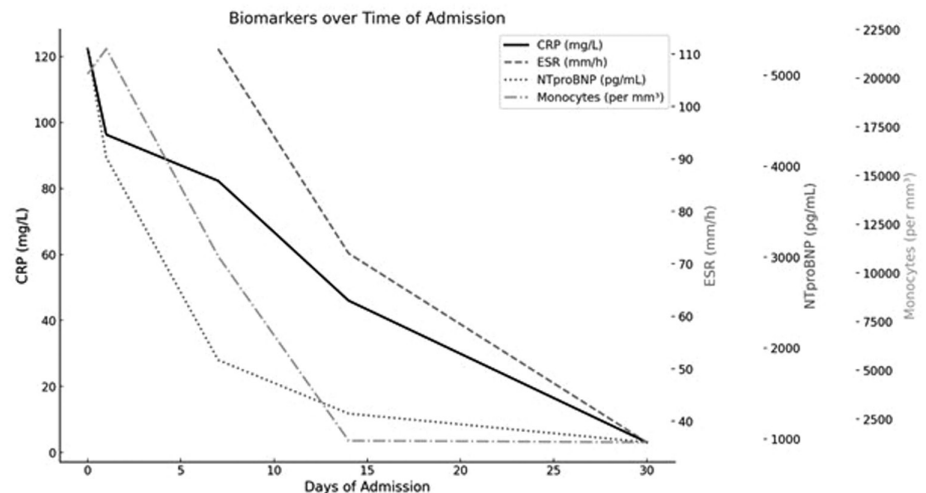


Figure 2. Biomarkers over time of admission, showing trends for CRP, ESR, NT-proBNP, and monocytes. CRP and ESR significantly decrease over the first 10 days, indicating reduced inflammation. NT-proBNP levels and monocyte counts also decline, suggesting improved cardiac function and immune response. Dual y-axes provide a comparative view over the 30-day admission period. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

genes related to innate immunity.⁵ The relationship between certain hematological malignancies and immune-mediated disorders has been recognized for decades.⁶ The association with autoinflammatory diseases is increasingly acknowledged following the description of VEXAS syndrome, often accompanied by myelodysplastic syndrome.⁷ Recently, there have been reported cases of patients with myeloid hematological malignancies presenting autoinflammatory manifestations in association with pathogenic *TET2* gene variants.⁸

TET2 is an epigenetic regulator of normal hematopoiesis, particularly myelopoiesis. Somatic mutations in this gene can trigger clonal hematopoiesis, promoting the development of hematological malignancies such as myelodysplastic syndromes or acute myeloid leukemias.^{1,9}

Recent studies indicate that *TET2* plays a crucial role in regulating innate immunity (Figure 3), which impacts both the initiation and resolution of the inflammatory response. Patients with loss-of-function *TET2* variants have increased proinflammatory cytokines (IL-1 and IL-6), leading to a systemic inflammatory state that favors the development of dysimmune phenomena.¹⁰ Molecular alterations, including *TET2* mutations, are present in 90% of patients with CMML.¹¹

Inflammatory serositis is one of the clinical manifestations that should raise suspicion of an autoinflammatory disease in the appropriate clinical context.¹² The patient exhibited inflammatory pleuropericarditis associated with a pathogenic *TET2* variant. The history of CMML, coupled with clinical and analytical evidence of inflammation, supported this

diagnosis. As with other autoinflammatory diseases, there is no serological marker to confirm clinical suspicion, so it is important to rule out other causes of inflammatory serositis.

Autoinflammatory episodes often respond to corticosteroids, but recurrences are common if used as monotherapy. Anti-IL1 agents have a higher response rate, and are preferred over typical immunosuppressants.¹³ In this case, the sequential combination of colchicine and anakinra was key in achieving clinical remission and normalization of inflammatory markers.

Recently, *TET2* variants have also been linked to myocardial dysfunction and heart failure. Experimental models have shown that *TET2* deficiency is associated with altered cardiac remodelling and function.⁴ Clonal hematopoiesis of indeterminate potential (CHIP) is characterized by somatic mutations in hematopoietic stem cells and is associated with increased proinflammatory cytokines. Loss of *TET2* function in myeloid cells with CHIP has been linked to an increased risk of atherosclerotic cardiovascular disease, possibly related to the activation of the IL-1B pathway and inflammasome.¹⁴

The CANTOS study demonstrated that patients receiving canakinumab had a lower risk of cardiovascular events and hospitalizations due to heart failure.¹⁵ The *TET2* gene was the most common site for somatic variation leading to CHIP in the CANTOS trial population, which indicates the role of *TET2* in the progression of atherosclerosis and the potential of anti-IL1 blockade as a therapeutic option.¹⁵ In the patient, the decrease in NT-proBNP following immunosuppressive treatment supports the hypothesis of myocardial dysfunction secondary to increased proinflammatory cytokines.

TET2 variations have also been linked to auto-immune diseases such as systemic lupus erythematosus and rheumatoid arthritis, as well as other inflammatory conditions such as gout and chronic obstructive pulmonary disease.¹⁰ The case suggests an autoinflammatory mechanism rather than an autoimmune one, based on clinical presentation and response to colchicine and anti-IL1 treatment.

In conclusion, pathogenic *TET2* variants in patients with myeloid hematological malignancies are becoming increasingly recognized as a cause of late-onset autoinflammatory diseases and cardiac dysfunction. Our case demonstrates the successful use of sequential colchicine and anti-IL1 in controlling these inflammatory complications, emphasizing the need for awareness and prompt treatment of *TET2*-related autoinflammatory manifestations in clinical practice. Further genetic studies are essential to identify the pathogenic mechanisms and other potential therapeutic targets in this patient population.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics Committee Approval was not required for the study.

Informed Consent: Written consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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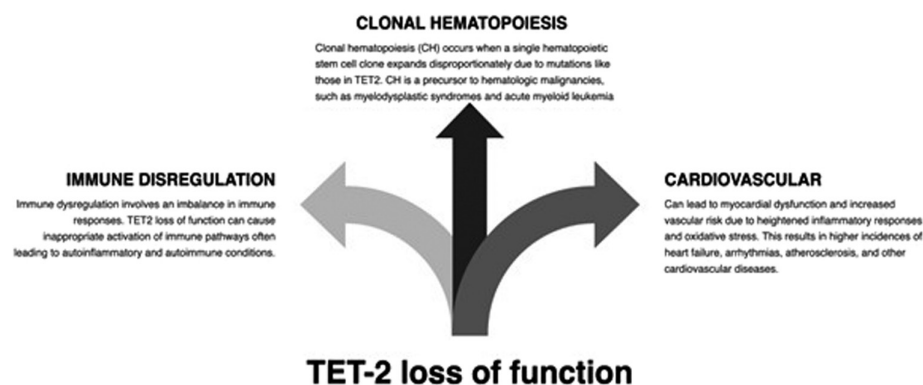


Figure 3. Consequences of *TET2* loss of function, showing immune dysregulation, clonal hematopoiesis, and cardiovascular complications. Immune dysregulation leads to immune-mediated phenomena, clonal hematopoiesis increases the risk of hematological malignancies such as myelodysplastic syndromes or acute myeloid leukemias, and cardiovascular events occur as a consequence of the inflammatory state and oxidative stress.

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