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LOW KLOTHO LEVELS AND HIGH PLATELET REACTIVITY AS PREDICTORS OF ADVERSE OUTCOMES IN MYOCARDIAL INFARCTION: A CASE-BASED INSIGHT. CLINICAL CASE

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Abstract

We describe a case of ST-elevation myocardial infarction in a 74-year-old patient with peripheral artery disease. Despite dual antiplatelet therapy with high-dose clopidogrel, stent thrombosis and recurrent infarction occurred, requiring escalation to ticagrelor. Additionally, a low level of Klotho protein was detected, associated with increased risk of complications. This case highlights the importance of platelet function testing and emerging biomarkers for individualized therapy.

Keywords: *Klotho protein, ST-segment elevation myocardial infarction, renal dysfunction, aggregometry, residual platelet reactivity*

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Резюме

НИЗКИЙ УРОВЕНЬ KLOTHO И ВЫСОКАЯ РЕАКТИВНОСТЬ ТРОМБОЦИТОВ КАК ПРЕДИКТОРЫ НЕБЛАГОПРИЯТНЫХ ИСХОДОВ ПРИ ИНФАРКТЕ МИОКАРДА: АНАЛИЗ НА ОСНОВЕ КОНКРЕТНОГО СЛУЧАЯ

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Описан случай инфаркта миокарда с подъёмом ST у 74-летнего пациента с поражением периферических артерий. На фоне резистентности к клопидогрелю развился тромбоз стента и повторный инфаркт, что потребовало эскалации терапии до тикагрелора. Дополнительно выявлен низкий уровень белка Klotho, ассоциированный с высоким риском осложнений. Случай подчёркивает значимость тестирования функции тромбоцитов и поиска новых биомаркеров для индивидуализации терапии.

Ключевые слова: *белок Klotho, инфаркт миокарда с подъемом сегмента ST, почечная дисфункция, агрегометрия, остаточная реактивность тромбоцитов.*

Для цитирования:

Жунуспекова А.С., Аккалиев М.Н., Аширов Б.А, Мансурова Д.А., Токбулатова М.О., Капакова М.А., Токтарова Ж.Ж., Нургалиева Д.Т. Низкий уровень klotho и высокая реактивность тромбоцитов как предикторы неблагоприятных исходов при инфаркте миокарда: анализ на основе конкретного случая. Клинический случай // Наука и Здравоохранение. 2025. Vol.27 (5), С.267-273. *doi 10.34689/SH.2025.27.5.031*

Түйіндеме

KLOTHO АҚУЫЗЫНЫҢ ТӨМЕН ДЕҢГЕЙІ МЕН ТРОМБОЦИТТЕРДІҢ ЖОҒАРЫ РЕАКТИВТІЛІГІ МИОКАРД ИНФАРКТІСІНДЕ ҚОЛАЙСЫЗ НӘТИЖЕЛЕРДІҢ ПРЕДИКТОРЛАРЫ РЕТІНДЕ: НАҚТЫ ЖАҒДАЙҒА НЕГІЗДЕЛГЕН ТАЛДАУ

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74 жастағы перифериялық артерия ауруы бар науқаста ST сегментінің көтерілуімен миокард инфарктісі жағдайы сипатталған. Жоғары дозадағы клопидогрелмен қос антитромбоцитарлық терапияға қарамастан, стент тромбозы және қайталама инфаркт дамыды, бұл тикагрелорға эскалацияны қажет етті. Сонымен қатар, асқыну қаупінің жоғарылауымен байланысты төмен Klotho ақуызының деңгейі анықталды. Бұл жағдай тромбоциттердің функциясын тестілеудің және жаңа биомаркерлерді қолданудың терапияны жекелендіру үшін маңыздылығын көрсетеді.

Түйінді сөздер: *Klotho ақуызы, ST сегментінің жоғарылауымен жүретін миокард инфарктісі, бүйрек қызметінің бұзылысы, агрегометрия, тромбоциттердің қалдық реактивтілігі.*

Дәйексөз үшін:

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Жунуспекова А.С., Аккалиев М.Н., Аширов Б.А, Мансурова Д.А., Токбулатова М.О., Капакова М.А., Токтарова Ж.Ж., Нургалиева Д.Т. Klotho ақуызының төмен деңгейі мен тромбоциттердің жоғары реактивтілігі миокард инфарктісінде қолайсыз нәтижелердің предикторлары ретінде: нақты жағдайға негізделген талдау. Клиникалық жағдай // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 267-273. *doi 10.34689/SH.2025.27.5.031*

Introduction:

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor remains the cornerstone of treatment in patients with acute coronary syndrome (ACS), particularly those undergoing percutaneous coronary intervention (PCI). However, a significant proportion of patients experience high on-treatment platelet reactivity (HTPR), which is associated with an increased risk of stent thrombosis and adverse cardiovascular events [1,2].

Clopidogrel, the most widely used P2Y12 inhibitor, exhibits substantial interindividual variability in its antiplatelet effect, influenced by factors such as genetic polymorphisms, drug interactions, and comorbidities [3]. In patients with peripheral artery disease (PAD), who often have diffuse atherosclerosis and heightened thrombotic risk, optimal platelet inhibition is critical for improving outcomes [4].

Recent studies have highlighted the potential role of morphogenetic protein Klotho as a biomarker of vascular aging, atherosclerosis, and cardiovascular risk. Low serum

Klotho levels have been linked to increased vascular calcification, endothelial dysfunction, and poor prognosis in patients with coronary artery disease [5,6].

This case report presents a patient with ST-elevation myocardial infarction (STEMI) and PAD who developed stent thrombosis despite intensified clopidogrel therapy. We discuss the utility of platelet function testing in guiding antiplatelet therapy, the role of genetic resistance, and the prognostic significance of Klotho levels in such high-risk patients.

Clinical case:

Patient: B., male, 74 years old. Medical Record No.: 13002

On October 8, 2024, the patient was urgently transported by the Emergency Medical Services (EMS) team to the Emergency Cardiology Department of the City Hospital with a diagnosis of: Coronary Artery Disease (CAD). Acute Coronary Syndrome (ACS) with ST-segment elevation (STEMI).

Complaints:

Pressing chest pain radiating to the lower jaw and left arm, pain duration >20 minutes, unrelieved by nitroglycerin, general weakness, shortness of breath.

Medical History: Atherosclerosis, Leriche syndrome, Bifurcation aorto-femoral bypass (2008), Left femoral-popliteal bypass (2008), Right lumbar sympathectomy (2009), Arterial hypertension (20 years), Obesity (BMI 30.1 kg/m²)

Pre-hospital Emergency Care (by EMS): Morphine 1.0 ml + 0.9% NaCl 10.0 ml, Isoket (isosorbide dinitrate) — 2 sprays sublingually, Aspirin 325 mg (chewed), Clopidogrel 300 mg orally.

Physical Examination on Admission: General condition: serious. Conscious and responsive. Hypersthenic body type. Pale skin and mucous membranes. Auscultation: harsh breathing sounds, diminished in lower lung fields. Respiratory rate: 18 breaths/min.Percussion: heart borders shifted to the left. Auscultation: muffled heart sounds, no murmurs, regular rhythm. Heart rate: 110 bpm, blood pressure: 180/100 mmHg, Moist tongue, not coated. Abdomen: normal shape, non-tender. Normal bowel and bladder function. No peripheral edema.

Electrocardiogram (ECG): Sinus tachycardia (HR 111 bpm). Left ventricular hypertrophy (LVH). Transmural myocardial infarction of the anterior, anteroseptal, and lateral walls of the left ventricle (Figure 1).

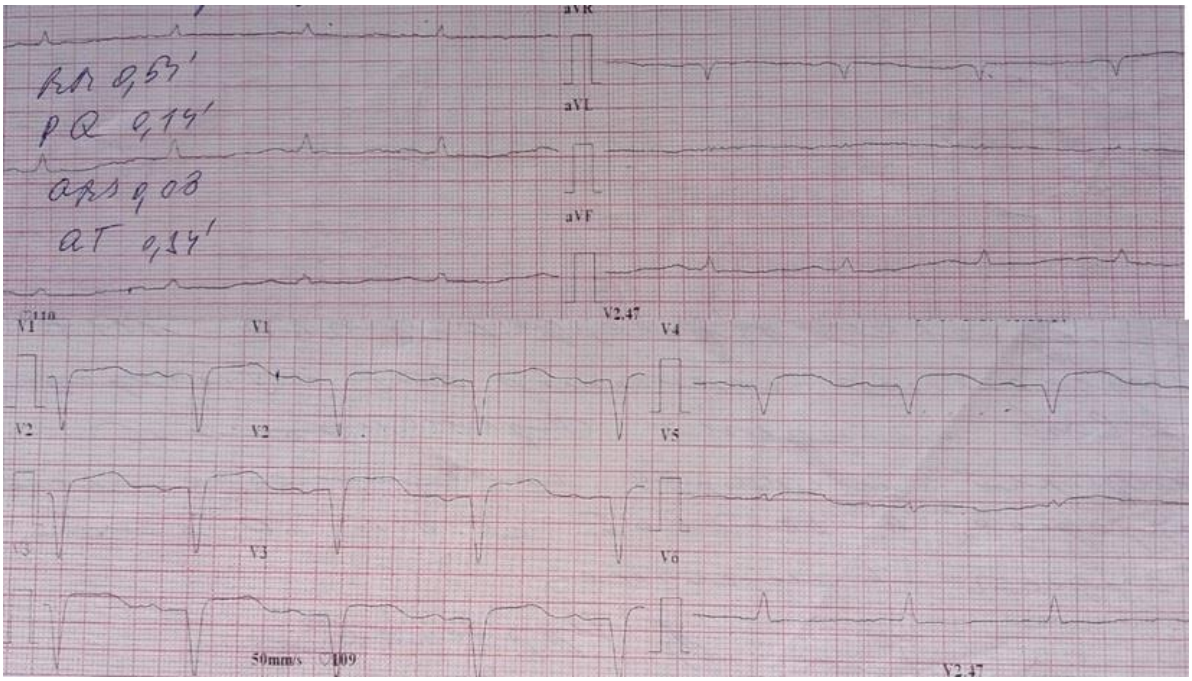

Figure 1. ECG on admission.

Laboratory Findings:

Complete Blood Count (CBC): Hemoglobin: 113 g/L, RBC: 4.1 x 10^9 /L, WBC: 8.2 x 10^9 /L, Platelets: 342 x 10^9 /L. Biochemistry: Total protein: 75 g/L, LDL: 3.86 mmol/L, HDL: 1.42 mmol/L, ALT: 13 U/L, AST: 23 U/L, CK-MB: 4 U/L, Total CK: 76 U/L, Total cholesterol: 7.0 mmol/L, Triglycerides: 2.32 mmol/L, Blood glucose: 4.8 mmol/L, Creatinine: 106 µmol/L, CRP: 4.0 mg/L, eGFR (CKD-EPI): 49 ml/min/1.73 m², Troponin I: 0.10 ng/ml, Klotho protein level: 42.9 ng/ml.

The patient was urgently transferred to the endovascular radiology laboratory for coronary angiography. Findings on Coronary Angiography: Left-dominant coronary circulation. Left Main Coronary Artery (LMCA): Smooth contours, patent. Left Anterior Descending artery (LAD): 70% stenosis in the proximal segment. Left Circumflex artery (LCx): Smooth contours, patent. Right Coronary Artery (RCA): Occlusion at the origin; distal segments are filled via intersystem collateral circulation (Figure 2).

Simultaneously, transluminal coronary angioplasty was performed with stent implantation in the proximal segment of the left anterior descending (LAD) artery. A drug-eluting stent measuring 3.5 x 24.0 mm was implanted. The result after (Figure 3).

After the endovascular intervention, a follow-up ECG was performed: Sinus rhythm with a heart rate of 70 bpm. Horizontal position of the electrical axis (EAX). Mild R-wave progression in leads V1–V3. Following revascularization, standard therapy was initiated, including dual antiplatelet therapy (DAPT) with aspirin in combination with clopidogrel at a maintenance dose of 75 mg/day.

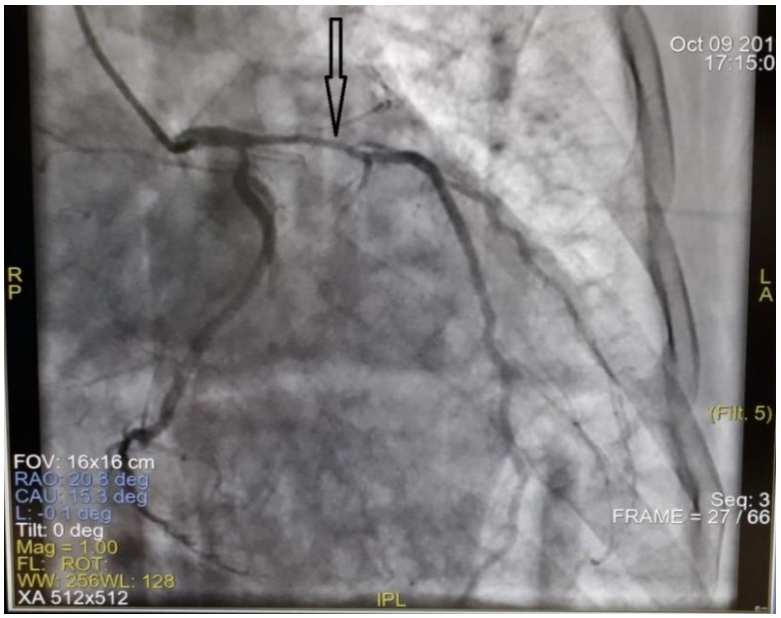

Figure 2. Coronary angiogram of the LAD basin before stenting.

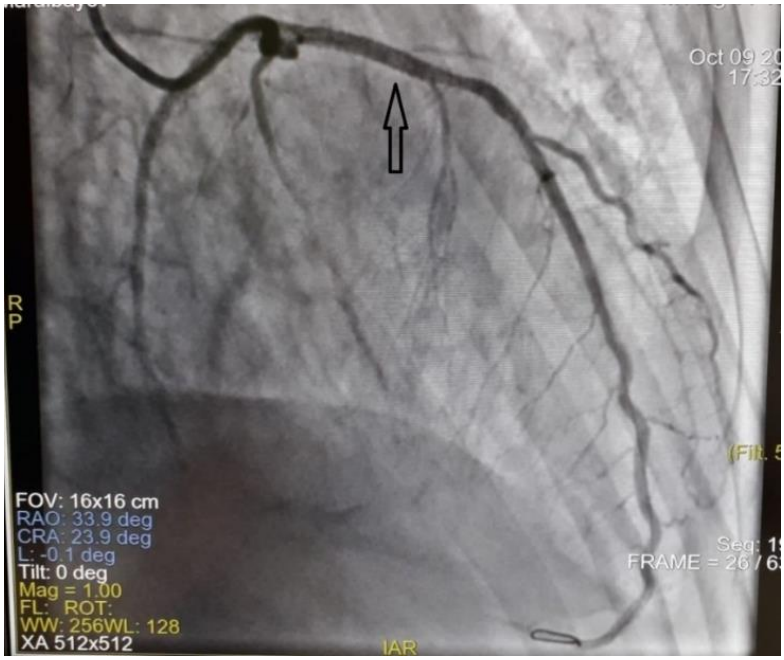

Figure 3. Coronary angiogram of the LAD territory after stenting.

On the morning of the following day, platelet aggregation activity was assessed. The VerifyNow P2Y12 Reaction Test (PRT) under dual antiplatelet therapy showed 82.5% inhibition and an area under the curve (AUC) of 75.1% (Figure 4). Given the high aggregation values, indicating inadequate platelet inhibition, the clopidogrel dose was increased to 150 mg/day to prevent stent thrombosis.

After 24 hours of hospitalization, the patient's condition showed negative dynamics, with new complaints of dizziness, speech disturbance, visual impairment, and nausea.

An emergency consultation with a neurologist was conducted, and cranial computed tomography (CT) was recommended. CT findings: CT signs of acute ischemic stroke in the left occipital lobe and cerebellum. Chronic cerebral microangiopathy. Mild external and internal non-occlusive hydrocephalus.

The patient was re-evaluated by a neurologist, and the following diagnosis was established: Acute Cerebrovascular Accident (CVA), ischemic stroke in the vertebrobasilar circulation, involving the left occipital lobe and cerebellar region (*atherothrombotic type*). Vestibuloatactic syndrome. Cerebral atherosclerosis. Arterial hypertension, grade III, risk category IV. Recommendations were provided.

On the eighth day of hospitalization, the patient's condition suddenly deteriorated. He began experiencing anginal chest pain, general weakness, and sweating. ECG findings: Sinus tachycardia with a heart rate of 115 bpm. Increased ST-segment elevation in leads V1–V4 (Figure 5).

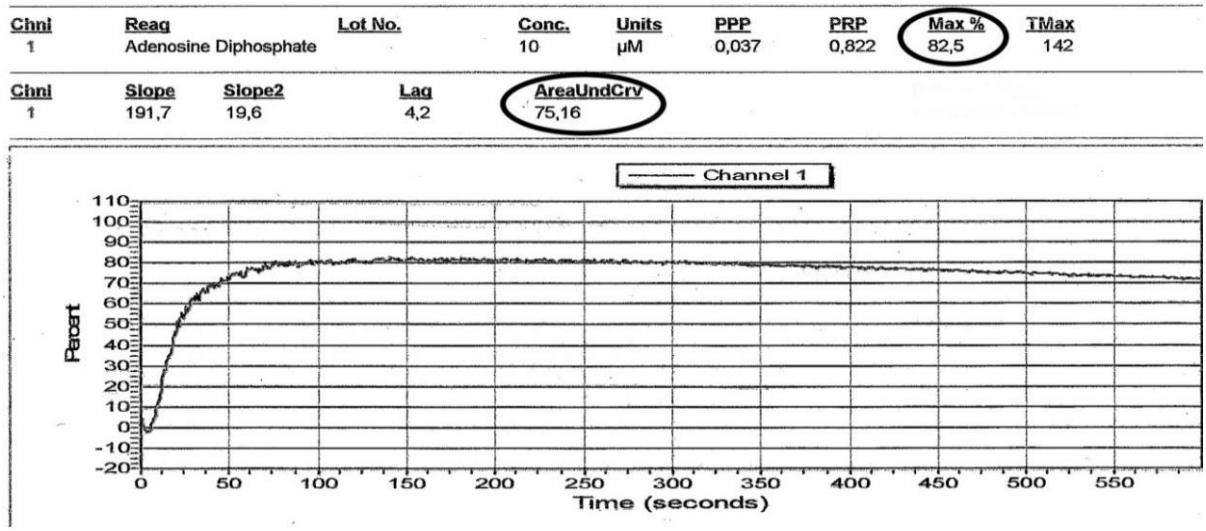

Figure 4. Aggregatogram.

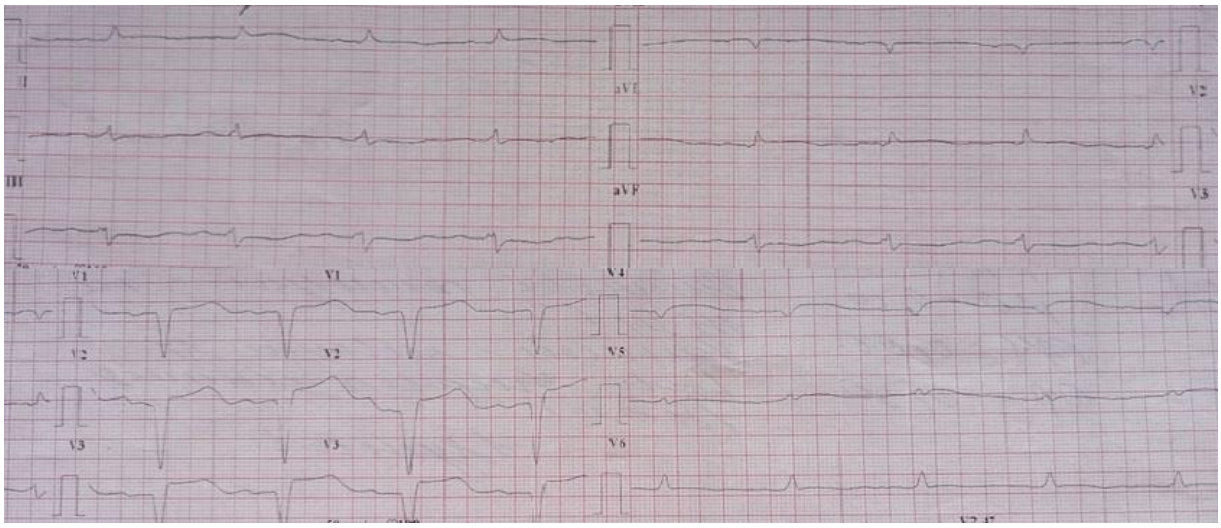

Figure 5. ECG in case of repeated angina.

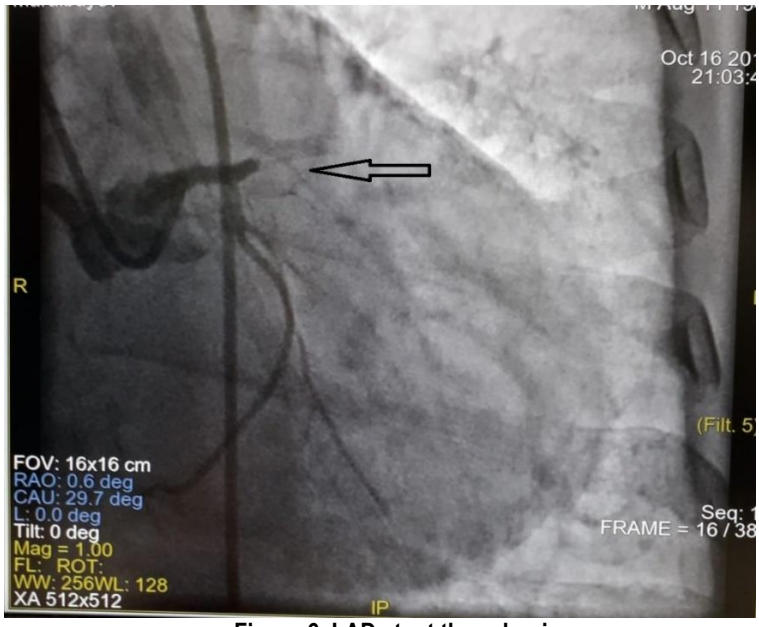

Figure 6. LAD stent thrombosis.

Laboratory findings: Troponin level increased to 4.67 ng/mL. Blood was simultaneously drawn to assess platelet reactivity (PRT).

Due to emergency indications, the patient was taken for repeat percutaneous coronary intervention (PCI). Coronary angiography (CAG) findings: Left main coronary artery (LMCA): patent. Left anterior descending artery (LAD): stent thrombosis in the proximal segment; distal flow not visualized. Left circumflex artery (LCx): 50% stenosis at the ostium (Figure 6). Procedure performed: repeat stenting of the LAD with a drug-eluting stent measuring 3.5 × 18.0 mm.

Platelet aggregation testing revealed high on-treatment platelet reactivity (HTPR).

Under the doubled dose of clopidogrel, the P2Y12 Reaction Test (PRT) showed:82.5% platelet reactivity. Area under the curve (AUC): 75.1% (Figure 7).

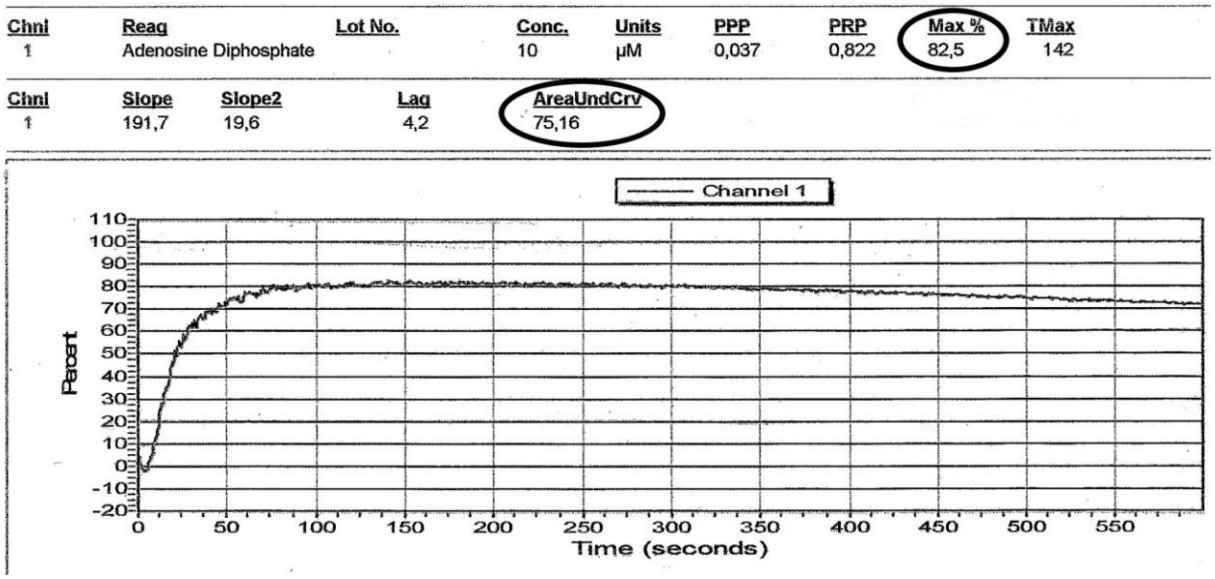

Figure 7. Aggregatogram. ORT against the background of a double dose of clopidogrel 150 mg.

The patient's results were comparable to the reference values of platelet aggregation in healthy volunteers not taking antiplatelet agents (82.1% vs. reference interval 76.8–97.2%, and AUC 75.1% vs. reference interval 68.8–90.4%). The presence of high on-treatment platelet reactivity (HTPR) despite antiplatelet therapy indicates the ineffectiveness of the current antiplatelet agent.

As a result, antiplatelet therapy was escalated, and the patient was switched to ticagrelor 90 mg twice daily. Follow-up platelet function testing was performed 3 days later, showing: Platelet reactivity of 51.1%, AUC:31.6% (Figure 8).

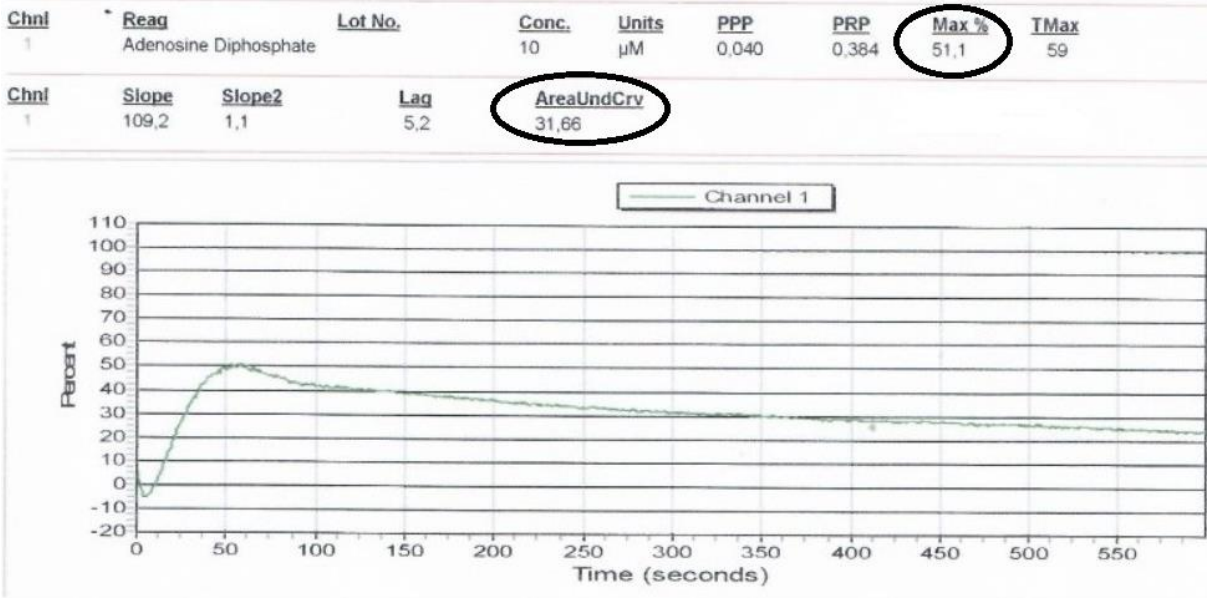

Figure 8. Aggregatogram. Platelet reactivity after escalation therapy.

Thus, in our patient with coronary artery disease involving not only the coronary vessels but also the lower limb arteries, and with clinical presentation of STEMI, stent implantation in the LAD while on a double dose of clopidogrel was complicated by the development of a recurrent type IVb myocardial infarction due to stent thrombosis.

Following antiplatelet therapy escalation, platelet reactivity significantly decreased, indicating the effectiveness of the new therapy.

The low level of the morphogenetic protein Klotho is consistent with findings from other authors, who have demonstrated that reduced Klotho levels are directly associated with the severity of atherosclerosis and calcification of the heart and vessels.

Discussion

This clinical case highlights several crucial considerations in the management of high-risk patients with ST-elevation myocardial infarction (STEMI) and concomitant peripheral artery disease (PAD), particularly regarding personalized antiplatelet therapy and emerging biomarkers such as Klotho.

The patient underwent primary percutaneous coronary intervention (PCI) with stent implantation in the left anterior descending artery (LAD). Despite receiving a double maintenance dose of clopidogrel (150 mg/day), he experienced subacute stent thrombosis and recurrent type IVb myocardial infarction. High on-treatment platelet reactivity (HTPR) was confirmed by platelet function testing, a finding that has been repeatedly associated with increased risk of stent thrombosis and adverse cardiovascular outcomes [7,8].

HTPR in this context likely reflects clopidogrel resistance, which may be mediated by genetic polymorphisms in the CYP2C19 gene, particularly the *CYP2C19* *2/*2 and *2/*3 loss-of-function alleles [9]. Although genotyping was not performed in this case, the platelet function assay (VerifyNow) showed clear evidence of pharmacological ineffectiveness, justifying the escalation of antiplatelet therapy. Switching to ticagrelor, a direct-acting reversible P2Y12 inhibitor, significantly reduced platelet reactivity and area under the curve (AUC), confirming its efficacy in overcoming clopidogrel resistance [10].

The patient's low level of circulating Klotho protein is also of particular interest. Klotho is an anti-aging and vasculoprotective protein involved in regulation of endothelial function, calcium-phosphate metabolism, and inhibition of vascular calcification. Low Klotho levels have been shown to correlate with increased arterial stiffness, atherosclerotic plaque burden, and adverse cardiovascular outcomes in both the general and chronic kidney disease populations [11,12]. In a study by Semba et al., lower serum Klotho levels were associated with higher risk of cardiovascular events and mortality in older adults [13]. These findings support the hypothesis that Klotho may serve not only as a marker of vascular aging, but also as a predictive biomarker in acute coronary syndromes.

Furthermore, the occurrence of an acute ischemic stroke in the vertebrobasilar territory during hospitalization highlights the patient's diffuse atherosclerotic burden and vulnerable vascular state. This underscores the need for comprehensive secondary prevention strategies in patients with polyvascular disease, including more intensive antiplatelet regimens, lipid-lowering therapy, and possibly adjunctive approaches targeting vascular inflammation and calcification.

This case underscores the clinical value of platelet function testing in tailoring antiplatelet therapy, especially in high-risk individuals with evidence of inadequate

pharmacological response. It also brings attention to Klotho as a potential prognostic marker of cardiovascular vulnerability and as a possible future therapeutic target.

Conclusions

This clinical case:

- Demonstrates the importance of assessing platelet function in myocardial infarction, which allows for the personalization of antiplatelet therapy in patients with MI and peripheral artery disease (PAD);

- Indicates the need for genetic testing to identify clopidogrel resistance-related gene polymorphisms, as high platelet reactivity despite a double dose of clopidogrel may have contributed to stent thrombosis;

- Confirms that a low level of the morphogenetic protein Klotho serves as a predictor of cardiovascular complications and adverse events in patients with myocardial infarction and PAD.

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Conflict of Interest: *The authors declare no conflict of interest. We confirm that the materials presented in this article have not been published in any other printed publication.*

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