SUDDEN DECREASE IN EXERCISE TOLERANCE—A CASE STUDY ON ANOCA

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Abstract

This case study describes the evolution of a 45-year-old patient who presented to the hospital with a severe inferior respiratory tract infection. The interpretation of the electrocardiogram led to a reconsideration of the medical history and the identification of anginal pain, resulting in referral to the cardiology department. The investigations carried out (biochemical tests, stress test, and coronary angiography) established the diagnosis of angina with non-obstructive coronary arteries (ANOCA). The uniqueness of the case lies in the association of this diagnosis with a combination of traditional cardiovascular risk factors (hypertension, dyslipidemia) and non-traditional factors (chronic inflammation, psychosocial stress). The average duration for establishing the diagnosis of ANOCA remains prolonged, contributing to the decrease in patient's quality of life. This case emphasizes the need for more efficient educational, diagnostic, and therapeutic strategies. It is essential to increase public awareness regarding the importance of addressing subtle symptoms that can be mistaken for the effects of aging and to reduce diagnostic delays in order to improve cardiovascular prognosis.

Key Words: microvascular angina, ANOCA, bacterial pneumonia, lipoprotein(a).

INTRODUCTION

Non-obstructive coronary artery disease (ANOCA) is a complex and often underdiagnosed clinical entity, encompassing subtypes such as microvascular angina and vasospastic angina under the same spectrum. Unlike obstructive coronary artery disease, characterized by significant atherosclerotic stenoses that are hemodynamically relevant, ANOCA involves mechanisms such as endothelial dysfunction or vasospasm, leading to myocardial ischemia despite the absence of atherosclerotic disease (Pepine, 2023). Young patients, particularly females without traditional risk factors, present with a higher incidence of this pathology (Anderson et al., 2019).

This condition is associated with significant morbidity and a reduction in the quality of life, primarily due to persistent and debilitating symptoms. Although the risk of major cardiovascular events was initially thought to be lower than in obstructive coronary artery disease, recent studies have shown otherwise (Skalidis et al., 2023) (Mehta et al., 2022). The reduction in functional flow reserve, which occurs in microvascular dysfunction, has been associated with diastolic dysfunction and a higher incidence of subsequent heart failure with preserved systolic function (Taqueti et al., 2018). Additionally, the predictability of angina-like pain onset is lower, occurring at rest as well as with exertion, and the symptoms are harder to control with current therapy (Smilowitz et al., 2023). All of these factors contribute to a vicious cycle, as patients reduce physical activity in order to avoid triggering symptoms. Over time, this may also increase the risk of progression of atherosclerotic disease, further reducing functional status (Shaw et al., 2006).

In a 2023 study by Martha Gulati et al., a major decline in the quality of life of these patients was noted using a questionnaire. Most of the respondents (40.4%) experienced symptoms for 1 to 5 years, and nearly half had symptoms for 1 to 10 years before receiving a diagnosis. A percentage of 77.8% had previously been informed that their symptoms were not cardiac in origin. Reported symptoms were varied, but 92.9% mentioned chest pain, pressure, or discomfort, and 80.6% reported dyspnea, which was classified as an angina equivalent (Gulati et al., 2023).

According to the European Society of Cardiology (ESC) guidelines published this year, once chronic coronary syndrome is suspected, ischemia requires objective documentation through stress or exercise tests, which may exacerbate the patient's

symptoms or show newly-emerged ECG changes suggestive of ischemia (Vrints et al., 2024). However, these tests cannot provide information about the mechanism of ischemia or quantify its severity, requiring further investigations such as CT coronary angiography or percutaneous transluminal coronary angiography. Although the recommendations are quite clear, literature evidence shows that there are numerous imperfections in this diagnostic algorithm. In a study of 96 women, the exercise test showed a sensitivity of 31% and a specificity of only 52% (Lewis et al. & National Heart, 2005) (Skelly et al., 2016).

The management of these patients differs from the traditional management of obstructive coronary artery disease. Treatment requires individualization, considering the wide range of mechanisms involved in the development of this syndrome. The relationship between psychological stress and the onset of angina in ANOCA requires better management of everyday stress, while physical exertion, dosed according to the level at which angina develops, is encouraged, although it may initially cause significant discomfort (Raija Tyni-Lenne et al., 2006). Regarding pharmacological therapy, the 2024 ESC guidelines are not as clear. Beta-blockers, calcium channel blockers, long-acting nitrates, and other antianginal medications such as ranolazine and trimetazidine are mentioned. The difficulty for controlling the symptoms requires adjusting medication according to the patient's needs (Vrints et al., 2024).

This case study presents the situation of a 45-year-old patient who initially presented with a lower respiratory tract infection, which led to a detailed cardiovascular evaluation and ultimately the diagnosis of ANOCA. The case highlights the importance of interdisciplinary collaboration and the need for increased awareness of ANOCA among clinicians, especially in patients with atypical presentations or unexplained ischemic changes on the electrocardiogram (ECG).

Another objective of this study is to highlight the low proportion of functional coronary tests performed currently in medical practice. The fact that the patient does not have an atherosclerotic stenosis should not automatically imply cessation of the path towards a correct diagnosis.

METHODOLOGY

Relevant keywords ["chronic coronary syndrome," "ANOCA," "microvascular angina," "vasospastic angina," "endothelial dysfunction," "atherosclerotic disease," "lipoprotein(a)"] were used to search through current literature from PubMed, Elsevier, and Google Scholar. Twenty-one articles were included from the approximately 200 reviewed. These articles, published in the last 10 years in English and Romanian, focused on meta-analyses, clinical studies, and practice guidelines.

The literature review involved a detailed comparison of the case specifics with previously reported data. A narrative approach was used to identify both similarities and discrepancies relevant to diagnosis and management.

The diagnosis was established according to the clinical presentation, ECG, biomarkers, exercise test, coronary angiography, and the evaluation of emerging factors [e.g., lipoprotein(a)].

In accordance with ethical standards, informed consent from the patient and approval of the study protocol by the ethics committee of "Dunărea de Jos" University of Galați were obtained.

Case presentation

A 45-year-old female patient presented to the emergency department of the Pneumoftiziology Hospital in Galați, complaining of fever, chills, initially dry, then productive cough, and fatigue. The symptoms had started insidiously about two weeks ago, with a progressive worsening in the last few days. After the investigations, an acute bacterial pneumonia diagnosis was established, and the patient received etiological and symptomatic treatment.

Among the investigations performed was an ECG, which showed repolarization changes in the anterior territory, suggestive of ischemia. Although the patient did not report any chest pain in the initial anamnesis, upon re-evaluation, she mentioned that she had started experiencing an anginal type of pain both at rest and during physical activity, beginning about a year ago. Prior to the onset of chest pain, the patient was physically active and regularly participated in mountain hiking. The onset of pain forced

her to significantly reduce her physical activity, which considerably impacted her quality of life.

Upon discharge, treatment with lipid-lowering agents, negative inotropes, and antiplatelets was initiated, following the 2024 European Chronic Coronary Syndrome Guidelines, and a cardiology examination was recommended for further investigations.

As per the pulmonologist's recommendation, the patient attended a cardiology consultation at the Military Emergency Hospital "Aristide Serfioti" in Galați. In addition to the anterior chest pain, the patient did not report other symptoms. During anamnesis, the patient revealed that her mother and sister both have cardiovascular conditions, although she was unsure about the specifics of their conditions. The physical examination showed an enlarged abdomen due to adipose tissue.

An ECG performed in the cardiology department (shown in Figure 1) still revealed ST-segment depression in the anterior leads. An echocardiogram was also performed, which showed a minor functional aortic regurgitation, without any wall motion abnormalities.

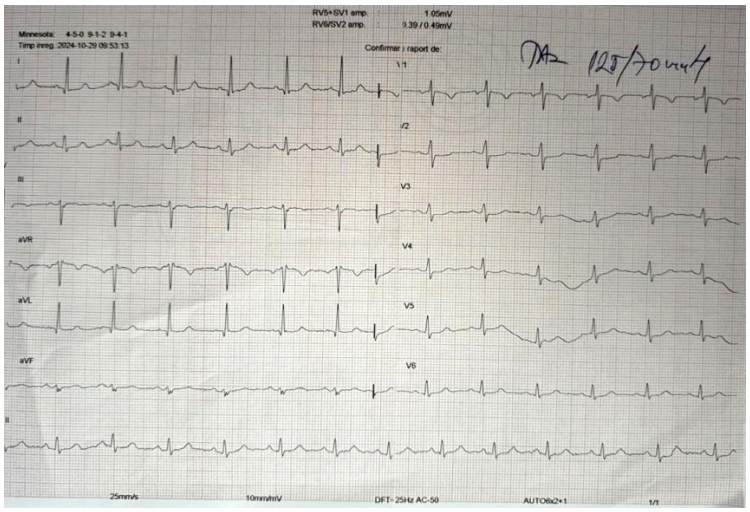
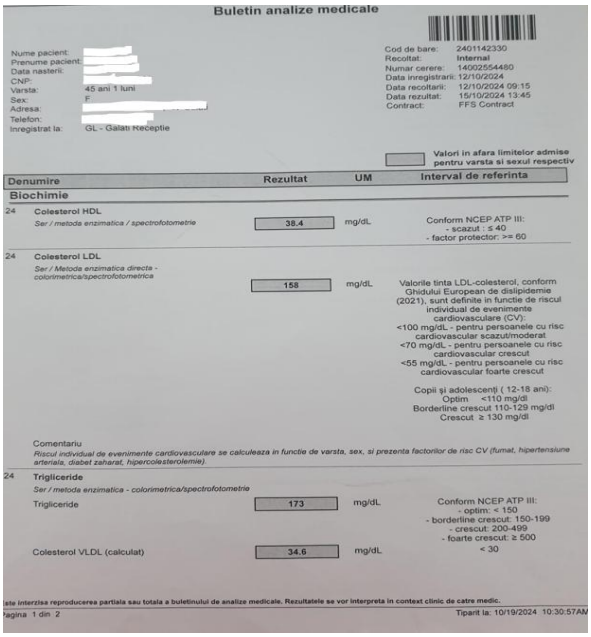


Figure 7: ECG at the presentation in cardiology department: sinus rhythm, 84/min, horizontal ST segment depression in leads V2-V4, artifacted trace.

Fortunately, the patient was also advised to measure LDL cholesterol, triglycerides, and lipoprotein(a) at baseline, before starting the treatment. The results are shown below in Figure 2 and Figure 3. These can be compared with the values from the tests performed on the day of the cardiology consultation, as presented in Figure 4. It is worth mentioning that the time interval between the two measurements was 17 days, during which the patient began treatment with atorvastatin 40 mg daily. A decrease

in LDL cholesterol was observed, from a value of 158 mg/dL to 84 mg/dL, and a decrease in triglycerides, from 173 mg/dL to 145 mg/dL, with an associated increase in HDL cholesterol from 38 mg/dL to 43 mg/dL. The lipoprotein(a) value was 30 mg/dL and was not measured afterward.



Buletin analize medicale

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Prenume pacient: [redacted]
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CNP: [redacted]
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Sex: F
Adresa: [redacted]
Telefon: [redacted]
Inregistrat la: GL - Galati Receptie

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Data rezultat: 15/10/2024 13:45
Contract: FFS Contract

Valori in afara limitelor admise pentru varsta si sexul respectiv

Denumire	Rezultat	UM	Interval de referinta
Biochimie			
24 Colesterol HDL *Ser / metoda enzimatica / spectrofotometrie*	38.4	mg/dL	Conform NCEP ATP III: - scazut : ≤ 40 - factor protector: >= 60
24 Colesterol LDL *Ser / Metoda enzimatica directa - colorimetrica/spectrofotometrica*	158	mg/dL	Valorile tinta LDL-colesterol, conform Ghidului European de dislipidemie (2021), sunt definite in functie de riscul individual de evenimente cardiovasculare (CV): <100 mg/dL - pentru persoanele cu risc cardiovascular scazut/moderat <70 mg/dL - pentru persoanele cu risc cardiovascular crescut <55 mg/dL - pentru persoanele cu risc cardiovascular foarte crescut Copii și adolescenți (12-18 ani): Optim <110 mg/dl Borderline crescut 110-129 mg/dl Crescut ≥ 130 mg/dl
Comentariu *Riscul individual de evenimente cardiovasculare se calculeaza in functie de varsta, sex, si prezenta factorilor de risc CV (fumat, hipertensiune arteriala, diabet zaharat, hipercolesterolemie).*			
24 Trigliceride *Ser / metoda enzimatica - colorimetrica/spectrofotometrie*			
Trigliceride	173	mg/dL	Conform NCEP ATP III: - optim: < 150 - borderline crescut: 150-199 - crescut: 200-499 - foarte crescut: ≥ 500
Colesterol VLDL (calculat)	34.6	mg/dL	< 30

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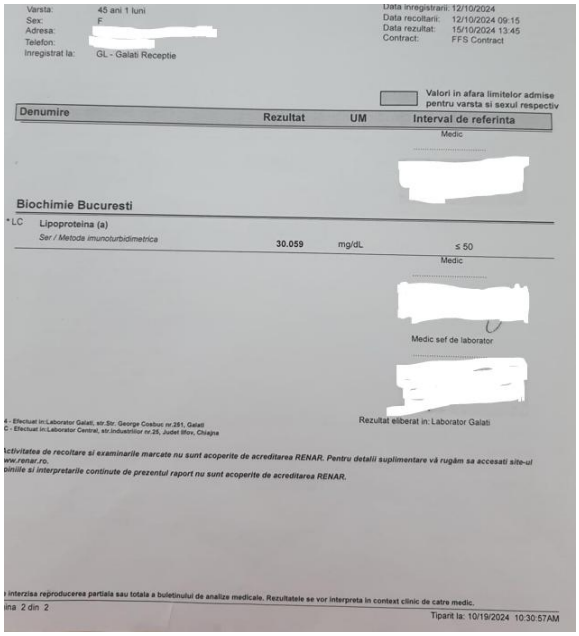
Figure 8: The blood tests recommended by the pulmonologist and performed by the patient immediately after discharge from the pulmonology department..



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Denumire	Rezultat	UM	Interval de referinta
			Medic [redacted]
Biochimie Bucuresti			
* LC Lipoproteina (a) *Ser / Metoda imunoturbidimetrica*	30.059	mg/dL	≤ 50 Medic [redacted] Medic sef de laborator [redacted]

Rezultat eliberat in: Laborator Galati

- Efectuat in:Laborator Galati, str.Str. George Cosbuc nr.251, Galati
C - Efectuat in:Laborator Central, str.Industriilor nr.25, Judet Ilfov, Chiajna

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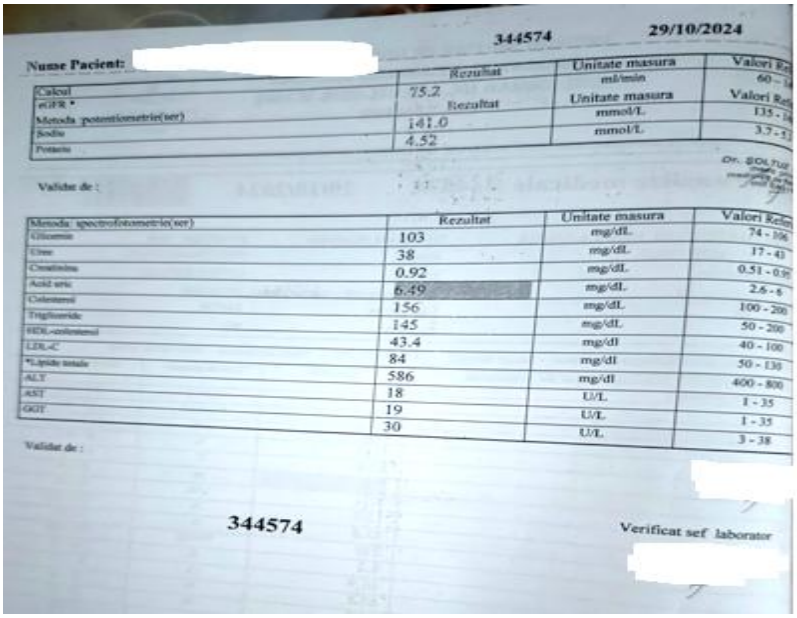
Figure 9: The blood tests recommended by the pulmonologist and performed by the patient immediately after discharge from the pulmonology department.



344574 29/10/2024

Nume Pacient: [redacted]

	Rezultat	Unitate masura	Valori Ref
Calcul eGFR *	75.2	ml/min	60 -
Metoda potentiometrie(ser)	Rezultat	Unitate masura	Valori Ref
Sodiu	141.0	mmol/L	135 -
Potasiu	4.52	mmol/L	3.7 -

Validat de :

Dr. SOLTUZ

Metoda: spectrofotometrie(ser)	Rezultat	Unitate masura	Valori Ref
Glicemie	103	mg/dL	74 - 106
Uree	38	mg/dL	17 - 43
Creatinina	0.92	mg/dL	0.51 - 0.95
Acid uric	6.49	mg/dL	2.6 - 6
Colesterol	156	mg/dL	100 - 200
Trigliceride	145	mg/dL	50 - 200
HDL-colesterol	43.4	mg/dl	40 - 100
LDL-C	84	mg/dl	50 - 130
*Lipide totale	586	mg/dl	400 - 800
ALT	18	U/L	1 - 35
AST	19	U/L	1 - 35
GGT	30	U/L	3 - 38

Validat de :

344574

Verificat sef laborator [redacted]

Figure 10: The blood tests at the time of presentation to the cardiology department, after approximately two weeks of treatment with atorvastatin 40 mg.

Given the symptoms and ECG changes, a treadmill exercise test was performed to evaluate the suspicion of coronary artery disease, which was found to be positive for ischemia (Figure 5 and Figure 6), with the onset of anterior chest pain, increased ST segment depression, and excessive blood pressure rise to approximately 192/69 mmHg, in the context of a normotensive individual. The exercise capacity, quantified using metabolic equivalents, revealed a value of 62% of the predicted capacity.

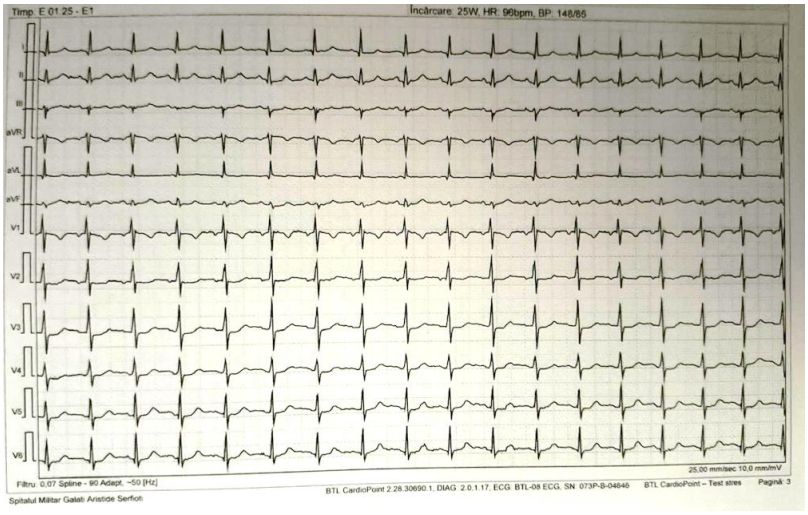


Figure 11: Exercise ECG trace, during exertion

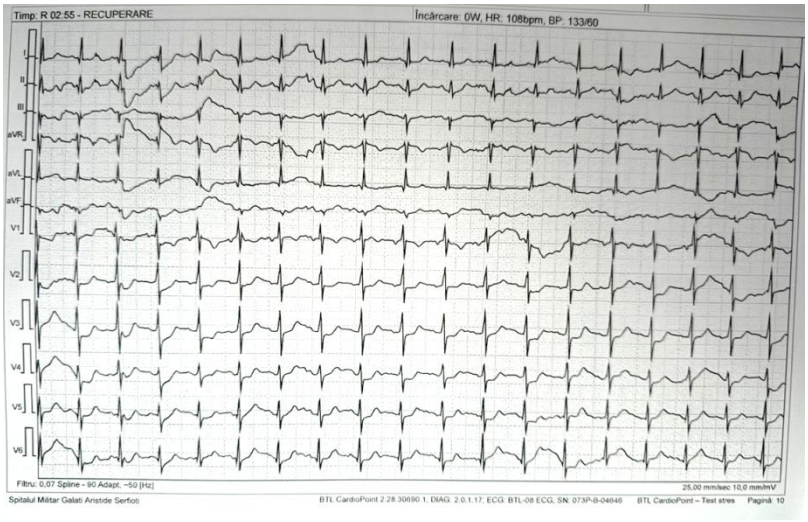


Figure 12: Exercise ECG during the recovery period: Increase of horizontal ST segment depression in the anterior leads.

Given the presence of high-risk criteria, coronary angiography was recommended to assess the patency of the coronary arteries. The angiography did not reveal any significant hemodynamically relevant lesions, and the epicardial coronary arteries were patent. Therefore, the final diagnosis was microvascular angina.

DISCUSSIONS

The severity of the pneumonia prompted the patient to seek care in a hospital setting—a measure that had likely been delayed, as had occurred over the past year since symptom onset, and as noted in other studies in the literature (Gulati et al., 2023). This case represents a fortunate example where a simple yet correct interpretation of an ECG ultimately led to the diagnosis of a condition with significant impact on the patient's quality of life.

Given the patient's symptoms, guideline-based treatment was initiated immediately after discharge from the pulmonology department, aiming to alleviate symptoms and reduce the risk of major cardiovascular events (Vrints et al., 2024). Initial investigations directed the diagnosis towards chronic coronary syndrome, a finding further supported by the exercise test. However, while the test indicated the presence of ischemia, it did not provide detailed information about its mechanism or the severity of the disease.

Although the patient did not belong to an older age group, the presence of genetic predisposition, symptomatology, and high cardiovascular risk criteria identified during

the exercise test justified the recommendation for coronary angiography. This was indicated both to assess coronary artery patency and for the possibility of percutaneous intervention with stent placement in the event of significant lesions.

The absence of hemodynamically significant coronary lesions required adjustments to the therapeutic plan, focusing on the management of reccurent symptoms. The time elapsed between the patient's discharge from the Pneumology Hospital and the cardiology consultation was approximately two weeks. During this period, although the patient was receiving nebivolol, a selective beta-blocker intended to reduce myocardial oxygen consumption, anginal pain persisted. In this context, initiating treatment with a non-dihydropyridine calcium channel blocker was recommended to alleviate anginal symptoms, alongside lipid-lowering therapy to reduce long-term cardiovascular risk (Vrints et al., 2024).

ANOCA, as emphasized in the introduction, is a spectrum rather than a standalone disease. Improving treatment success rates necessitates additional testing during coronary angiography, such as fractional flow reserve (FFR), coronary flow reserve (CFR), and optical coherence tomography (OCT) (Lee et al., 2022). These tests refine the diagnosis by providing insights into the pathophysiological mechanism and thus enable tailored medication adjustments. However, the procedure's duration significantly increases, and these features are not available in all interventional cardiology centers. In a study conducted by Sarena La et al. from January 2012 to December 2018, 7,555 patients suspected of angina pectoris underwent elective coronary angiography. The study revealed that an exceptionally low proportion (6%) of ANOCA patients underwent functional angiography, despite evidence of myocardial ischemia and patent coronary arteries. Over 90% of the patients in this cohort thus received empirical treatment without verifying its applicability to individual pathophysiological characteristics. Unsurprisingly, approximately one-third of the treated patients in the study continued to report frequent anginal chest pain (La et al., 2023).

Although the patient's coronary arteries were patent, baseline blood tests revealed dyslipidemia and hypertriglyceridemia. These abnormalities, correlated with an overweight status (BMI = 26.8 kg/m^2), indicate an early metabolic syndrome, which

is associated with a markedly elevated cardiovascular risk (Lemieux et al., 2020).

Moreover, the lipoprotein (a) level of 30 mg/dL, while within the laboratory reference range, has been shown in recent studies to be associated with increased mortality independently of other risk factors (Vinci et al., 2023; Iannuzzo et al., 2021). It has been demonstrated that this level is genetically inherited, conferring elevated cardiovascular risk, and the patient reported a family history of cardiovascular conditions in her sister and mother, although the exact pathologies could not be specified (Duarte Lau F et al., 2022).

The uniqueness of this case lies in the association of ANOCA with traditional cardiovascular risk factors such as dyslipidemia, hypertriglyceridemia, and hyperuricemia, alongside more recently studied factors like lipoprotein (a).

Ischemia in ANOCA can act synergistically with potential atherosclerotic stenoses, amplifying the severity of ischemia (Dimitriadis et al., 2024). Given that atherosclerosis is an inevitable consequence of aging, reducing cardiovascular risk through pharmacological interventions and lifestyle modifications becomes essential, especially in the presence of ANOCA. The patient's young age is a presumed advantage, as she is currently free from the consequences of atherosclerotic disease, as demonstrated by the coronary angiography. However, without timely medical attention, necessary interventions would not have been implemented, leading to progressive worsening of the symptoms and progression of the disease in the coming years.

CONCLUSIONS

To improve the management of patients with ANOCA, measures are needed from both the patient and specialist perspectives. For patients, it is essential to undergo regular medical check-ups, avoiding visits to the doctor only in cases of acute conditions or when the disease has reached an advanced stage. For specialists, it is crucial to conduct dedicated studies to better understand the mechanisms of ANOCA and implement strategies that facilitate the performance of necessary tests for an accurate diagnosis. This would allow for the prescription of targeted treatment, increasing the chances of therapeutic success, reducing hospitalisations, and improving patient's quality of life. Furthermore, this approach would contribute to lowering healthcare

system costs, thus being more economically beneficial compared to the current empirical treatments.

Lipoprotein (a) remains an insufficiently understood topic. While most existing studies explore its relationship with obstructive coronary artery disease, the possibility of an association with ANOCA should not be overlooked, requiring further investigation.

In conclusion, a sudden decrease in exercise tolerance in a physically active, previously asymptomatic patient, associated with the onset of new chest pain, should not be simply attributed to the aging process. Such symptoms should be thoroughly investigated to rule out a cardiovascular condition like ANOCA, which could benefit from early diagnosis and treatment.

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