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CASE REPORT
Coronary intervention

First demonstration of implication of hereditary alpha-tryptasaemia in vasospastic angina: a case report

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Background Vasospastic angina is a common condition. In cases of poor therapeutic response, less common causes should be explored.

Case summary A 50-year-old woman with vasospastic angina was diagnosed with significant fluctuation in response to treatment without explanation that led to the suspicion of an allergic phenomenon. A diagnosis of hereditary alpha-tryptasaemia was made, and introduction of a second-generation H1-antihistamine has enabled effective control of previously treatment-resistant vasospastic coronary disease.

Discussion The case shows the first time the involvement of hereditary alpha-tryptasaemia in vasospastic angina. Future pathophysiological investigations will be needed to further explore the connection between these two pathologies.

Keywords Vasospastic angina • MINOCA • Cardiac MR • Case report

ESC curriculum 3.1 Coronary artery disease • 3.2 Acute coronary syndrome • 3.4 Coronary angiography

Learning points

- When a patient with vasospastic angina shows significant fluctuations in response to treatment without a clear explanation, hereditary alpha-tryptasaemia may be detected through elevated basal serum tryptase levels (≥8 µg/L) and genetic testing. In this context, the addition of a second-generation H1-antihistamine can significantly improve the treatment response.

Introduction

Vasospastic angina, also called Prinzmetal angina, causes resting chest pain with ST segment elevation.[1] This common and underdiagnosed condition results in angina or myocardial infarction with no obstructive coronary artery disease. The pathophysiology of the disease involves endothelial dysfunction and coronary smooth muscle hypercontractility.[2] This condition can be primary but is more often triggered by irritants such as smoking, cocaine, or certain medications (e.g. 5-fluorouracil, triptans, and beta-blockers). In rarer cases, hyper activation of inflammatory pathways may be involved as with hypereosinophilia or allergic reaction as with Kounis syndrome. The latter is defined as the occurrence of acute coronary syndrome, such as coronary vasospasm, acute myocardial infarction, and stent thrombosis due to allergy or hypersensitivity and anaphylactic reaction.[3] However, other rare causes of immuno-allergic disorders

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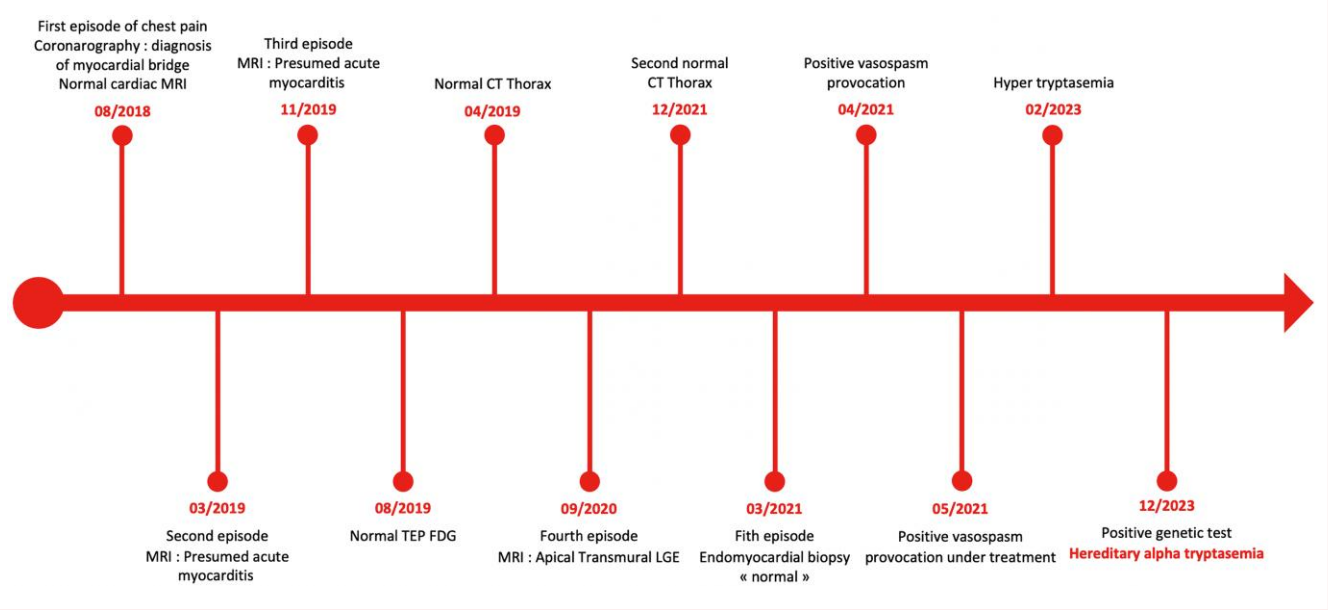
have been described. To the best of our knowledge, this article presents the first reported case of severe and recurrent coronary vasospasm in a context of hereditary alpha-tryptasaemia (HAT), an additional disease implicated in immuno-allergic disorders.

Summary figure



Case presentation

A 50-year-old woman with no cardiovascular risk factor and with a history of four episodes of acute myocarditis presented another episode of chest pain. The previous invasive coronary angiogram was normal and cardiac magnetic resonance performed in a distinct centre presented late gadolinium enhancements (LGEs) classified as compatible with a myocarditis pattern. Over the course of the fifth episode, patient presented substernal chest pain, and physical examination showed haemodynamic stability and no signs of right or left heart failure. Heart sounds were regular and without murmurs. The electrocardiogram indicated a sinus rhythm with deep negative T-waves in V4–V6. Transthoracic echocardiography revealed preserved left ventricular ejection fraction. Cardiac magnetic resonance was performed and showed myocardial infarction with no obstructive coronary arteries (MINOCA) and ischaemia—rather than myocarditis-related LGE (*Figure 1A–E*). A new invasive exploration with coronary vasospasm provocation using acetylcholine was performed, which indicated severe vasoreactivity with complete obstruction of the left anterior descending artery (LAD) resolving after intracoronary nitrates (*Figure 1F and G*, see Supplementary material online, *Videos S1* and *S2*). Diagnosis of vasospastic angina was established, and vasodilator therapy was initiated (verapamil extended-release 240 mg, nicorandil 0.5 tablet of 10 mg nicorandil twice daily) in addition to statin (atorvastatin 80 mg) and aspirin 75 mg.

The provocative test was repeated at 1 month to evaluate treatment efficacy and indicated the persistence of a severe LAD vasospasm resolving after intracoronary nitrates (see Supplementary material online, *Videos S3* and *S4*). The disease was stabilized by treatment intensification (+molsidomine 2 mg three times daily), but follow-up revealed considerable fluctuations in treatment efficacy depending on the days without identifiable triggers, ultimately leading to a diagnosis of refractory vasospastic angina (increased molsidomine 4 mg three times daily, and nicorandil 10 mg 0.5 twice daily, +transdermal patch delivering nitroglycerine 15 mg).

Therefore, rarer causes of spastic angina were investigated. Hypereosinophilia was excluded. In this context of fluctuating treatment efficacy, periodic exposure to an allergen was suspected. A consultation with an allergist was requested. In light of this unusual coronary hyperactivity, we investigated the possibility of type 1 Kounis syndrome (allergic or hypersensitivity reaction).[4] Histamine, the main amine released during allergic reactions, can provoke coronary arterial spasm manifested as angina pectoris. The effects of histamine on cardiac function are mediated via H1- and H2-receptors on coronary arteries. Chest pain could then be attributed to coronary arterial spasm resulting from histamine release in the allergic context. In the present case, tryptasaemia was abnormal [basal serum tryptase (BST): 19.8 ng/mL, normal < 8 μg/L] despite the absence of an allergic context. So, in this context of elevated BST, mast cell-associated diseases must be investigated. However, the patient showed no evidence of main cause of mast cell-associated diseases (clonal mast cell disease or mast cell activation, or connective tissue manifestations in relation with Ehlers–Danlos syndrome type III). Finally, we decided to investigate rare cause mast cell-associated diseases. Hereditary alpha-tryptasaemia, a genetic condition, was considered. Genetic testing was positive (increased TPSAB1 copy number). Following diagnosis of HAT, a second-generation H1-antihistamine was introduced (rupatadine 10 mg). The patient did not experience any recurrence of anginal symptoms with stable treatment (aspirin, statin, verapamil extended-release 240 mg, and transdermal patch delivering nitroglycerine 15 mg).

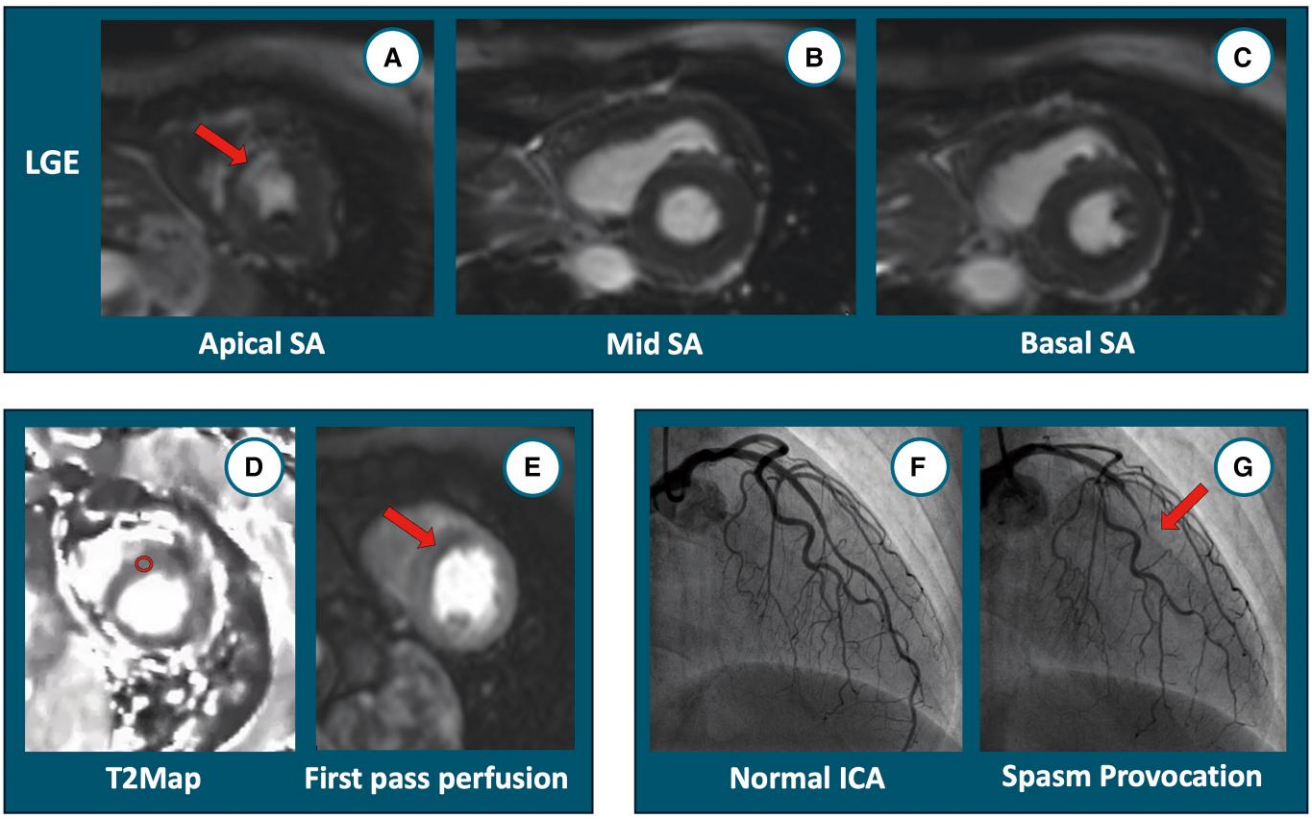


Figure 1 Cardiac magnetic resonance presents transmural late gadolinium enhancement on apical short axis (*A*), but not in mid (*B*) or basal (*C*) short axis. T2 mapping is high at 57 ms (*D*). Perfusion defect on the first pass sequence (*E*). Invasive coronary angiography shows an absence of significant stenosis at rest (*F*) but a complete obstruction of the LAD is present on provocative test (*G*).

Discussion

This case illustrates, for the first time, the involvement of HAT which should be sought in treatment-resistant vasospastic coronary disease. Hereditary alpha-tryptasaemia is an autosomal dominant genetic trait that consists in the alteration of the germline number of copies of the TPSAB1 gene encoding the alpha isoform of tryptase and a common cause of elevated BST.[5] Elevated BST levels are present in 4%–6% of the general population, and symptomatic persons with HAT suffer from a complex constellation of symptoms (exhaustion, depressive episodes, sleep disturbances, and memory impairment, gastrointestinal symptoms such as irritable bowel, nausea, and reflux, flushing, itch, urticaria, and anaphylaxis). Basal serum tryptase is characterized by constitutive release of tryptases from mast cells. Hereditary alpha-tryptasaemia arises from additional germline copies of the gene TPSAB1 encoding the α-isoform of tryptase. These lead to increased constitutive release of α-tryptases and thus to elevated BST levels. Patients with a BST concentration ≥ 8 μg/L may have HAT and should be referred to a mast cell centre for further investigation. Elevated BST concentration is associated with increased prevalence of multiple predominantly functional and clinical phenotypes, including recurrent cutaneous symptoms, symptoms of autonomic instability, and functional gastrointestinal disorders, as well as systemic venom reactions and connective tissue abnormalities. However, the expressivity of the HAT phenotype is extremely variable.[5] One hypothesis is that the pathological potency of HAT is caused by active heterotetrametric α/β-tryptase and that these are more abundant in patients with a higher α/β ratio. Tryptase heterotetramers may cleave cell surface receptors or secreted proteins, thereby altering biological functions.[6] Heterotetramers can reduce the threshold for vibratory-induced mast cell degranulation[7] and increase histamine which promotes spasm mediated via H1- and H2-receptors on coronary arteries. This can lead to endothelium-independent and dependent dysfunctions at both the epicardial ang microcirculatory levels considering the described links between epicardial spastic angina and concomitant microcirculatory damage.[8]

In the present case, we report the association between vasospastic angina and HAT. Interestingly, upon interrogation, we found other symptoms (exhaustion, depressive episodes, sleep disturbances, gastrointestinal symptoms) that also improved with H1-antihistamine medication. In this specific case, the fluctuating efficacy of the angina treatment led us to suspect an allergic phenomenon. While the coronary effect of histamine release by mast cell degranulation is suggested here, future investigations will be needed to better understand pathophysiological.

Conclusion

This case highlights the importance of investigating HAT in patients with vasospastic angina and unexplained treatment fluctuations.

A confirmed diagnosis should prompt the addition of a second-generation H1-antihistamine.

Lead author biography

Gilles Barone-Rochette is an interventional cardiologist specialist in invasive and non-invasive imaging of coronary artery disease who works for Grenoble Alpes Hospital in France. He received his medical degree at the Grenoble Alpes University in 2007. He obtained a doctor of engineering for Health, Environment and cognition from the University of Grenoble-Alpes. He was promoted to Professor in 2015.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Consent: Consent for publication was obtained from the patient, in accordance with the COPE best practice guidelines.

Conflict of interest. G.B.-R. has received research grants from Merck Sharp and Dohme, Abbott Vascular, and Pfizer, and consulting fees from Bayer, General Electric, Boehringer Ingelheim, and MEDIS Medical Imaging, Abbott Vascular, Novo Nordisk, Sanofi, Novartis, and Amgen. The remaining authors have no competing interests to declare.

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Data availability

The data underlying this article are available in the article and in its online Supplementary material.

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