Q-myocardial Infarction on the Background of Undifferentiated Connective Tissue Dysplasia: Pathogenetic "Paradoxes" and "Crossovers"

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Abstract

Acute myocardial infarction (MI) is an important public health problem. Modern cardiology studies the role of such a premorbid background as undifferentiated connective tissue dysplasia (UCTD) in the pathogenesis of coronary heart disease (CHD) and MI in particular. Despite a large number of studies, the biochemical pathogenetic links of MI development against the background of UCTD remain unexplored. That is why our study aimed to analyze the stigmas of dysembryogenesis, coagulogram parameters, and platelet and uric acid (UA) levels as the most expected factors in the pathogenesis of MI with UCTD. The level of platelets in the peripheral blood of patients with UCTD (182.0 [161.0–265.0] x 109/l) did not differ reliably (but it was still significantly lower) from that in patients without UCTD [230.0 [206.0–309.0] x 109/l) (p>0.05). In particular, in 26 patients (57.8%) with UCTD, it was below the reference value. In those patients, who also have a large number of UCTD markers (10 or more), the stigma of "easy hematoma formation with insignificant damage" was most common. The level of UA in patients with Q-IM with UCTD was higher than normal and reliably higher than in the group without dysplasia (383.60 ± 33.82 vs. 292.11 ± 28.56, p<0.05). Increasing the level of UA provokes the activation of inflammatory processes in the coronary arteries, and leukocyte-lymphocytic infiltration of their tunica media, which, even at a low platelet level, leads to a cascade of mutually aggravating pathological changes that converge at the level of multivector endothelial damage.

Keywords: Myocardial infarction, Undifferentiated connective tissue dysplasia, Platelets, Uric acid

INTRODUCTION

Cardiovascular disease (CVD) is associated with coronary heart disease (CHD), which is a leading cause of death and increases the risk of cardiovascular complications [1, 2]. A special niche alongside traditional risk factors for coronary artery disease and in particular myocardial infarction (MI) (atherogenic dyslipidemia, hypertension, diabetes) is today occupied by hyperuricemia and disorders of vascular and platelet hemostasis [3]. On the other hand, modern cardiology studies the role in the development and progression of CHD in such a premorbid background as undifferentiated connective tissue dysplasia (UCTD) [4-6]. UCTD is a genetic condition characterized by defects in fibers and the main substance of connective tissue and its cellular composition, leading to disruption in the formation of organs and systems, having a progressive course, and determining the characteristics of associated pathologies [7].

From a clinical point of view, the cardiovascular manifestations of the UCTD are the most significant, as they provoke the involvement of compensatory mechanisms that, against the background of metabolic processes in the UCTD, lead to rapid myocardial depletion, up to MI and severe heart failure [4, 8].

Due to the prevalence of UCTD among people of working age in the general population (particularly more than 50% of the population in environmentally unfavorable regions of Eastern Europe), the investigation of the biochemical properties of Q-IM in UCTD is relevant [9, 10]. Although cardiovascular markers of UCTD are currently well studied,

some authors note changes in blood cells (the liquid form of connective tissue), particularly platelets, in people with UCTD [9, 11]. Therefore, we decided to highlight and analyze the stigmas of dysembryogenesis, coagulogram parameters, platelet, and uric acid (UA) levels as one of the most anticipated and important factors in the pathogenesis of MI with UCTD; this was the purpose of our study.

MATERIALS AND METHODS

90 male patients with verified Q-MI, aged 26 to 83 years, mean age (57,68 ± 1,27) years, who were hospitalized in the cardiology department No1 "Vinnytsya Regional Clinical Medical and Diagnostic Center for Cardiovascular Pathology" (Vinnytsya, Ukraine), were examined.

Verification of the diagnosis of Q-MI has been performed based on a positive result of the troponin test and elevated levels of cardio-specific enzymes in the presence of pain and relevant ECG changes, taking into account international standard criteria [10] and according to medical care protocol for patients with acute coronary syndrome [12].

To achieve the goal of the study, patients were divided into two groups. The main group included 45 men with MI on the background of UCTD, aged from 26 to 75 years, mean age (of 55,87 ± 1,66) years. The comparison group consisted of 45 patients with MI without UCTD (number of phenotypic and visceral stigmas of UCTD – 5 and less), aged from 36 to 83 years, mean age (of 58,49 ± 1,49) years.

Exclusion criteria were concomitant nosologies that affected the structural and geometric parameters of the heart muscle, clinical features, and development of CHD complications: hypertension, obesity, diabetes, other severe comorbidities (chronic obstructive pulmonary disease, malignant neoplasms), primary and secondary mitral valve prolapse.

The main group and the comparison group were represented by the age of patients, risk factors, and features of family history of CVD.

All patients underwent clinical, instrumental and laboratory studies, followed by statistical processing of the obtained data. In particular:

- Survey of patients. All subjects were surveyed using a specially designed original questionnaire based on the phenotypic map of Glesby in the modification of Martinov and co-authors [9, 13]. The questionnaire included 54 positions of microanomalies. The number of phenotypic and visceral stigmas of UCTD was counted, based on examination. The diagnosis of UCTD was established by detecting 6 or more positions of microanomalies [10].
- Somatometric examination (analysis of the following anthropometric features by the method of Bunak modified by Shaparenko [14], such as body weight, body length, torso length, neck length, chest-length, lower length limbs, head circumference, chest circumference) [9].
- Instrumental methods: All patients underwent electrocardiographic examination (ECG) in 12 standard leads on an electrocardiograph "Heart Screen 112 D" (Hungary) to diagnose focal changes in the ventricular myocardium, and primary screening for arrhythmias and conduction disorders. Abnormalities of the kidneys (dystopia, ectopia, partial doubling of the pelvis and ureters, cysts, nephroptosis) and gallbladder (single or multiple constrictions, inflections, and deformation of the gallbladder) were determined using ultrasound apparatus General Electric «Logic-7» (Vivid – 3) (USA).
- laboratory methods. All patients underwent general clinical and biochemical studies in the accredited clinical and biochemical laboratory of the "Vinnytsya Regional Clinical Medical and Diagnostic Center for Cardiovascular Pathology" (attestation certificate № 003892).

Determination of UA and platelet levels was performed in the morning on an empty stomach. 12 hours before the study, alcohol, smoking, and eating were excluded, physical activity was restricted, and medications were excluded. A colorimetric enzyme method was used to determine the level of UA. The study was performed on a Gobas 6000 analyzer using the Roche Diagnostics test system (Switzerland). The following values of SC were taken as normal: 142.8-339.2 µmol/l. The level of platelets in the peripheral blood of all patients was determined by counting their number in the Goryaev chamber to exclude the possibility of the effect of platelet concentration changes on hemostasis parameters. The reference value of the platelet concentration was (170–400) x 10^9/l [15].

The design of our study provided that blood samples for analysis of coagulogram of patients included in the study, were taken directly in the reception department at the time of diagnosis verification; they did not take drugs that could affect the blood clotting process. To comprehensively assess the state of the coagulation part of hemostasis, the main indicators of the coagulogram of all patients were determined by the photometric (turbodensitometric) method on a semi-automatic 2-channel optical coagulometer "COA 2" ("LabiTec", Germany). In particular, we studied the indicators of prothrombin index (PI), international normalized ratio (INR), prothrombin time (PT), and fibrinogen. The values of PT and PI were studied by the method of A. J. Quick (1935) used a set of reagents "Techplastin tm-test" and "Thrombo-test" ("Technology-Standard", Russia-Ukraine). The reference values were considered: the level of PI - from 95 to 105%, PT - 11-14 seconds, and the level of INR - from 1.0 to 1.4. The concentration of fibrinogen in the blood was determined by the gravimetric method according to RA Rutberg (1961) by reagents from Biopharma (Ukraine) and Seppim S.A.

(France) on the Cobas Mira Plus biochemical autoanalyzer from Roche Diagnostics (Switzerland). Norm: 2 - 4 g/l [15].
- Data analysis was performed in SPSS Statistics v.23. Summary statistics of mean and standard error mean were used for quantitative measurements. The paired sample t-test was applied to assess the difference between variables. The p-value ≤ 0.05 was set as significant.

RESULTS AND DISCUSSION

Analysis of UCTD markers in the main group and the comparison group, conducted during somatometric examination and questionnaires of patients, found that the average number of stigmas in patients with UCTD was 8.44 ± 0.29, and in patients without UCTD - 4.47 ± 0.12. It should be noted that such phenotypic (radial-lacunar iris of the eye (30 patients, 66.7%), blue sclera (30 people, 66.7%), anomalies of the auricles (41 patients, 91.1%), predisposition to early caries (20 subjects, 44.4%), medial/lateral clinodactyly (39 subjects, 86.8%)) and visceral (varicose veins of the lower extremities (15 patients, 33.3%), mild hematoma formation with insignificant damage (10 people, 22.2%)) UCTD stigmas were detected significantly more often in the main group than in the comparison group (p<0.05). The obtained data are consistent with the results of other authors and our studies conducted on another cohort of patients [9, 10, 13, 16].

The study of coagulogram parameters and platelet levels revealed the following features **(Table 1)**.

Table 1. Coagulogram and platelet level in patients with acute myocardial infarction, (Med [25–75 %]) (n=90)

Indicators	Patients with UCTD (n=45)	Patients without UCTD (n=45)
Platelets, x 10^9/l	182 [161,0–265,0]	230,0 [206,0–309,0]
INR	1,02 [0,98–1,09]	0,98 [0,94–1,05]
PI, %	105,5 [98,1–111,1]	106,3 [98,8–111,9]
PT, sec	11,1 [10,5–11,8]	11,2 [10,7–11,8]
Fibrinogen, g/l	4,3 [4,1–4,6]	4,5 [4,2–4,7]

Thus, all changes in coagulogram parameters (PI, INR, PT, and fibrinogen) of patients in both groups were typical for MI and did not differ reliably. The level of platelets in the peripheral blood of patients in the main group (182.0 [161.0–265.0] x 10^9/l) did not exceed the norm and did not differ reliably from that in the comparison group (230.0 [206.0–309.0] x 10^9/l) (p > 0,05). However, it was still significantly lower than in patients without UCTD. In particular, in 26 patients (57.8%) it was below the reference value. This diagnostic finding caught our attention, and we decided to analyze the distribution of platelet levels depending on the number of UCTD stigmas in patients with Q-MI in the background of UCTD **(Figure 1)**.
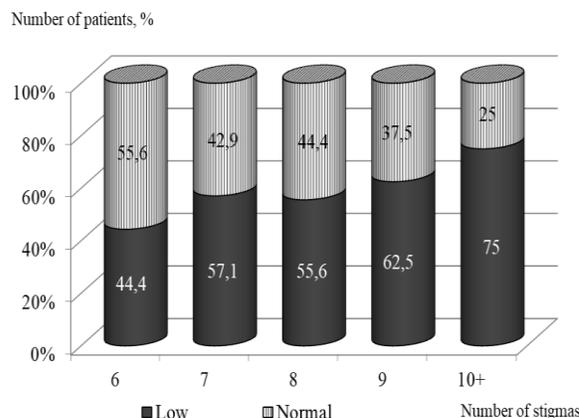

Figure 1. Distribution of platelet levels, depending on the number of UCTD stigmas, in patients of the main group.

The proportion of patients with low platelet levels has increased from 44.4% among people with six stigmas of UCTD, to 75% among patients with 10 or more stigmas. However, the increase in the percentage of such patients was not linear, these changes were not reliable (p>0.05) and only had a tendency.

It should be noted that among 12 patients with a large number of stigmas (10 or more) and, accordingly, low platelet levels, the largest number of patients (6 people) with such a visceral stigma of dysembryogenesis as "easy hematoma formation with insignificant damage" was found.

The obtained data suggest the role of even low platelet levels in the pathogenesis of MI in UCTD. This may be due to certain morphological deviations of platelets and purely dialectical laws of nature (in this context: quantity quality). To understand the mechanisms of coagulation hemostasis, it should be remembered that in the process of activation of platelets both anatomical and functional capabilities of platelets are important.

Therefore, it is known that the peripheral part of the platelet contains circularly oriented bundles consisting of 10-15 microtubules of actin and myosin microfilaments that support the typical shape of the platelet. Polymerization of microfilaments promotes the formation of processes for the interconnection of platelets and their binding to the surface of the damaged endothelium [17]. Because microfilaments are proteinaceous and have an amino acid composition synonymous with collagen and other connective tissue structures, changes in platelet function are expected in patients with UCTD. Decreased platelet levels and changes in their aggregation potential seem to lead to a weakening of arterial thrombogenesis, but deviations in the morphology of such platelets create the preconditions for endothelial microtrauma and ultimately enhance thrombogenesis [11, 17, 18]. Thus, changes in the cytoskeleton of platelets associated with depolarization of actin and disruption of calcium homeostasis in the cell are accompanied by disruption of their

pre-aggregation transformation and serotonin release. The phenomenon of "premature release" of calcium from platelets into plasma by centrifugation (swelling effect) is a marker of membranopathy with the formation of spontaneous aggregation on the background of high shear rate with increasing blood flow velocity in narrowed and deformed vessels. Persistent rheological disorders in angiodysplasias, abnormal chords, and duplicates of valves contribute to the formation of endothelial defects, and platelet hyper aggregation [5, 11, 13]. Hereditary defect in the synthesis of supporting contractile proteins - one of the components of the mechanism of platelet dysfunction in UCTD - may play a significant pathogenetic role in the development of hematomesenchymal dysplasia in patients with MI in the background of UCTD [11]. Thus, there is a pathogenetic paradox: on the one hand, reduced platelet level leads to a weakening of arterial thrombogenesis, and on the other - morpho-functional changes act as aggressive factors of endothelial damage at the histological level.

Comparative analysis of the average values of the level of UA in the blood of patients with Q-IM found that in patients of the main group the UA was higher than normal and reliably higher than in the comparison group (383.60 ± 33.82 vs. 292.11 ± 28.56, p<0.05). Our results are consistent with the work of Rak *et al.*, which clearly shows the association between elevated levels of UA in patients with UCTD with severe CVD, including hypertension. The number of studies on the UA's role in the development and progression of CVD is constantly growing [3, 19, 20].

Epidemiological studies have linked uricemia to CHD, stroke, hypertension, and heart failure. This connection occurs both in conditions of severe hyperuricemia and is maintained within normal values of serum levels of UA. Increased UA levels are an independently associated risk factor for cardiovascular pathology in both the general population and CVD patients, so serum UA testing is recommended as part of CVD screening [21-24]. It is known that UA is a catalyst for pro-inflammatory processes in the vascular endothelium (a direct damaging agent). However, indirectly due to increased blood pressure, elevated UA levels cause "hemodynamic vascular trauma", which leads to loss of basic endothelial functions, including antiplatelet and antiproliferative, which provokes a cascade of pathogenetic reactions and the development of CHD [20, 25].

Our analysis of coagulogram parameters, platelet, and UA levels revealed a certain phenomenon of "pathogenetic crossovers" in the context of endothelial damage. This phenomenon is that some people with MI and dysplasia have slightly lower than normal reference values of the average platelet level and are typical for MI coagulogram (slight hypercoagulable syndrome) at a much higher than average level of UA.

Currently, the existing hypothesis of impaired vascular-platelet hemostasis on the background of hyperuricemia in patients with MI and UCTD can be presented as follows [11, 25, 26]. Decreased platelet level with dysplastic changes eventually triggers a series of reactions that lead to increased arterial thrombogenesis. In turn, a steady increase in the UA level provokes the activation of inflammatory processes in the coronary arteries, and leukocyte-lymphocytic infiltration of their tunica media, which, even at a low platelet level, leads to a cascade of mutually aggravating pathological changes that converge at the level of multivector endothelial damage.

Conclusion

1. Decreased platelet levels associated with asymptomatic hyperuricemia may be an important component of the pathogenesis of MI and may be considered a significant risk factor in the presence of UCTD.
2. To confirm the hypothesis of impaired vascular hemostasis in the background of hyperuricemia in patients with MI and UCTD, it is necessary to conduct further genetic and histochemical studies, which will create the preconditions for a deeper and more comprehensive understanding of the problem.

References

1. Conclusions from the study of the global burden of disease in 2019. Cardiovascular diseases - the main cause of death of Ukrainians [Internet]. Public Health Center of the Ministry of Health of Ukraine; 2021 [cited 2021 Jan 04]. [In Ukrainian]. Available from: https://phc.org.ua/news/sercevo-sudinni-zakhvoryuvannya-golovna-prichina-smerti-ukrainciv-visnovki-z-doslidzhennya
2. Chiu IM, Barbayannis G, Cabrera J, Cosgrove NM, Kostis JB, Sargsyan D, et al. Myocardial Infarction Data Acquisition System (MIDAS 43) Study Group. Relation of Socioeconomic Status to 1-Year Readmission and Mortality in Patients with Acute Myocardial Infarction. Am J Cardiol. 2022;175:19-25. doi:10.1016/j.amjcard.2022.03.044
3. Rak N. Features of the clinical course of arterial hypertension combined with connective tissue dysplasia. Ph.D. thesis, Danylo Halytsky Lviv National Medical University. Danylo Halytsky Lviv National Medical University, Lviv. 2021. [In Ukrainian]
4. Chernykh MO. Coronary artery disease on the background of non-differentiated dysplasia of connective tissue: course peculiarities, aspects of diagnosis and prognosis. (Dys. kand. med. nauk). DVNZ Ivano-Frankiv. nats. med. un-t., Ivano-Frankivsk. 2016. [In Ukrainian]
5. Chernykh MO, Berezovskyi AM, Shamrai VA, Postolovskyi LYu. Clinical and morphological changes of the cardiovascular system in patients with cardioneurosis (neurocirculatory dystonia). Rep Vinnytsia Natl Med Univ. 2019;3(23):515-21. [In Ukrainian]
6. Lindahl B, Baron T, Albertucci M, Prati F. Myocardial infarction with non-obstructive coronary artery disease. EuroIntervention. 2021;17(11):e875-87. doi:10.4244/EIJ-D-21-00426. Erratum in: EuroIntervention. 2022 Apr 01;17(17):e1366.

7. Vershinina MV, Nechaeva GI, Gudilin VA. Relative cardiovascular risk in young patients with connective tissue dysplasia. Therapy. 2020;6:40-4. [In Russian]. doi:10.18565/therapy.2020.6.40-44

8. Hu M, Lu Y, Wan S, Li B, Gao X, Yang J, et al. Long-term outcomes in inferior ST-segment elevation myocardial infarction patients with right ventricular myocardial infarction. Int J Cardiol. 2022;351:1-7. doi:10.1016/j.ijcard.2022.01.003

9. Solyeyko OV, Rykalo NA, Osypenko IP, Soleyko LP. Syndrome of undifferentiated connective tissue dysplasia: from the concept of pathogenesis to treatment strategy. Tutorial. Vinnytsia, Ukraine: Nova Knyha; 2014. 168 p. [In Ukrainian]

10. Oleksandrivna CM, Vitaliivna SO, Petrivna SL, Borisivna YO, Prystupiuk M, Prystupiuk L, et al. Markers of Undifferentiated Connective Tissue Dysplasia in Female Patients with Acute Q-myocardial Infarction. Arch Pharm Pract. 2021;12(2):80-5. doi:10.51847/yMuzdZlE7y

11. Arsent'ev V, Pshenichnaya K, Suvorova A, Shabalov N. Clinical and pathogenetic aspects of disorders in the hemostasis system with connective tissue dysplasia in children. Pediatr- Zh G. N. Speranskogo. 2009;87(4):134-9. [In Russian]

12. Unified clinical protocol of emergency, primary, secondary (specialized), and tertiary (highly specialized) medical care and medical rehabilitation "Acute coronary syndrome with ST-segment elevation". Order of the Ministry of Health of Ukraine; 2014. Pub. L. No. 445. [In Ukrainian]

13. Nechaeva GI, Yakovlev VM, Konev VP, Druk IV, Morozov SL. Connective tissue dysplasia: main clinical syndromes, diagnosis formulation, treatment. Lechashchij vrach. 2008;2:22-5. [In Russian]

14. Shaparenko PF. Mathematical morphology - the way to objectify research. Principles of proportion, symmetry, structural harmony and mathematical modeling in morphology. Proceedings of the international symposium. Vinnytsia, Ukraine; 1997. p. 3-6. [In Russian]

15. Katerenchuk IP. Clinical interpretation and diagnostic value of laboratory parameters in general practice: a textbook. 4th ed. Kyiv: Medknyha; 2018. 228 p. [In Ukrainian]

16. Zaremba YeH, Rak NO, Zaremba OV, Zaremba-Fedchyshyn OV, Virna MM, Odnorih LO. Diagnostic criteria for undifferentiated connective tissue dysplasia in patients with arterial hypertension. Achv Clin Exp Med. 2020;2:49-54. doi:10.11603/1811-2471.2020.v.i2.1130

17. Lutsyk O, Chaikovskyi Yu. Histology. Cytology. Embryology: a textbook for students. Vinnytsia, Ukraine: Nova Knyha; 2020. 496 p. [In Ukrainian]

18. Xu Q, Wang LN, Zhao JY, Xiao YH, Du C. Effects of paeonol on proliferation and collagen synthesis of rat cardiac fibroblasts induced by aldosterone. Bangladesh J Pharmacol. 2021;16(2):42-8. Available from: https://www.banglajol.info/index.php/BJP/article/view/51605

19. Zaremba YeH, Zaremba OV, Rak NO, Prokosa MI, Chekh SR. Effect of quercetin on blood lipid spectrum, acute phase reactions, and uric acid levels in patients with hypertension combined with undifferentiated connective tissue dysplasia. Fitoterapiia. Naukovo-praktychnyi chasopys. 2018;3:26-30.

20. Casiglia E, Tikhonoff V, Virdis A, Masi S, Barbagallo C, Bombelli M, et al. Serum uric acid and fatal myocardial infarction: detection of prognostic cut-off values: The URRAH (Uric Acid Right for Heart Health) study. J Hypertens. 2020;38(3):412-9. doi:10.1097/HJH.0000000000002287

21. Borghi C, Bentivenga C, Cosentino ER. Uric acid and risk of myocardial infarction. A dynamic duo. Int J Cardiol. 2020;320:23-4. doi:10.1016/j.ijcard.2020.06.006

22. Abd El-Azeem NE, Elhefny M, Elzohri MH, Taher SM. Possibility of association of hypertension and ischemic heart disease with primary hyperuricemia. Curr Med Res Pract. 2020;5(1):109-14.

23. Lopez-Pineda A, Cordero A, Carratala-Munuera C, Orozco-Beltran D, Quesada JA, Bertomeu-Gonzalez V, et al. Association analysis between hyperuricemia and long term mortality after acute coronary syndrome in three subgroups of patients. Data Br. 2018;17:885-9. doi:10.1016/j.dib.2018.01.101

24. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol. 2019;234(10):16812-23. doi:10.1002/jcp.28350

25. Tian X, Zuo Y, Chen S, Wang A, Li H, He Y, et al. Associations between changes in serum uric acid and the risk of myocardial infarction. Int J Cardiol. 2020;314:25-31. doi:10.1016/j.ijcard.2020.03.083

26. Ösken A, Hacı R, Dinç Asarcıklı L, Arıkan ME, Onuk T, Ünal Dayı Ş, et al. Mean platelet volume/platelet count ratio as a predictor of stent thrombosis in patients with ST-segment–elevation myocardial infarction. Ir J Med Sci. 2021;190(3):1095-102. doi:10.1007/s11845-021-02626-y