Giant cell myocarditis in young woman diagnosed at the autopsy: a case report

Jan Hrudka[1], Ondřej Fabián[2,3], Róbert Petr[4], Tomáš Balík[5]

[1] *Department of Pathology, 3rd Faculty of Medicine, Charles University, University Hospital Kralovske Vinohrady, Prague, Czech Republic.*
[2] *Clinical and Transplant Pathology Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic.*
[3] *Department of Pathology and Molecular Medicine, 3rd Faculty of Medicine, Charles University, Thomayer Hospital, Prague, Czech Republic.*
[4] *Department of Cardiology, 3rd Faculty of Medicine, Charles University, University Hospital Kralovske Vinohrady, Prague, Czech Republic.*
[5] *Department of Anaesthesia and Intensive Care Medicine, 3rd Faculty of Medicine, Charles University, University Hospital Kralovske Vinohrady, Prague, Czech Republic.*

SUMMARY

Giant cell myocarditis (GCM) is a rare inflammatory disease of the heart that often affects younger patients. The clinical course is typically rapid with fulminant congestive heart failure. Prognosis is poor; the proper diagnosis is often rendered at the autopsy.

Herein, we present a prototypical case of this rare type of myocarditis, affecting a 44-year-old previously healthy woman who was referred to the intensive care department due to an acute onset cardiac arrest followed by resuscitation. The heart ultrasound and imaging examinations revealed a severe dysfunction and dilatation of both ventricles, without any significant finding in the coronary arteries. Twelve days after the initial presentation, the patient died due to congestive heart failure refractory to intensive therapy. The post-mortem histology of the heart revealed multiple small necrotic foci in the myocardium in both ventricles, with dense inflammatory infiltration with abundant multinucleated giant histiocytes, in line with a diagnosis of GCM.

The natural history, pathophysiology, and histological differential diagnosis is discussed, together with review of the relevant literature including uncommon and emerging units.

Keywords: giant cell myocarditis – congestive heart failure – autopsy

Obrovskobuněčná myokarditida u mladé ženy odhalená při pitvě: kazuistika

SOUHRN

Obrovskobuněčná myokarditida (OBM) je vzácné zánětlivé onemocnění srdce postihující často mladé osoby. Klinický průběh je typicky prudký**,** s fulminantním městnavým srdečním selháním. Prognóza je špatná, správná diagnóza je často stanovena až při pitvě.

V této práci popisujeme případ této vzácné myokarditidy postihující 44letou, do té doby zdravou ženu, která byla hospitalizována na klinice anesteziologie a resuscitace po náhlé srdeční zástavě a mimonemocniční resuscitaci. Echokardiografie a zobrazovací vyšetření prokázala těžkou dysfunkci a dilataci obou komor, bez významného nálezu na koronárních tepnách. Dvanáct dní po přijetí pacientka zemřela pod obrazem městnavého srdečního selhání refrakterního na terapii. Při histologickém vyšetření srdce po pitvě byla v myokardu obou komor nalezena mnohočetná nekrotická ložiska s hustou zánětlivou celulizací s účastí hojných obrovských vícejaderných histiocytů, v souladu s diagnózou OBM.

Článek diskutuje patologickou anatomii, patofyziologii a histologickou diferenciální diagnostiku této vzácné choroby, součástí je i přehled recentní literatury popisující neobvyklé a nové jednotky.

Klíčová slova: obrovskobuněčná myokarditida – městnavé srdeční selhání – pitva

Cesk Patol 2021; 57(3): 174–178

Giant cell myocarditis (GCM) is a rare inflammatory disease of the heart that often affects young or middle-aged previously healthy persons. In a large multicenter registry, the age at the first onset varies between 16 – 69 years with an average age 42 years (1); however, GCM has been reported even in an infant (2). Most patients (≥75%) present with rapid-onset congestive heart failure. Less common symptoms include ventricular tachycardia, chest pain or complete heart block (3,4). The disease course is rapid, with a median time of 3 weeks from symptom onset to need of hospitalization (5). Prognosis is generally poor; GCM often escapes diagnosis until heart transplantation or autopsy.

In this paper, we present an archetypal case of GCM in a young woman with unexpected cardiac arrest, in which the proper diagnosis was determined in the autopsy. Differential diagnostic considerations focused on myocarditis histopathology are discussed, including uncommon and emerging units.

✉ ***Correspondence address:***
Jan Hrudka, M.D., Ph.D.
Department of Pathology 3rd Faculty of Medicine, Charles University
University Hospital Kralovske Vinohrady, Prague
Šrobárova 1150, 100 34 Praha 10
tel.: +420 724 579 183
e-mail: jan.hrudka@lf3.cuni.cz

CASE DESCRIPTION

A 44-year-old Caucasian woman was referred to the hospital by emergency because of an acute onset cardiac arrest. The emergency was called by the patient's family who was woken up by an unrest and grunting in the night. Police arriving prior to the emergency performed resuscitation and defibrillation. Emergency continued in resuscitation, which was followed by asystole and ventricular fibrillation, further defibrillation and orotracheal intubation. There was no significant medical history

prior to this event. The patient was referred to the cardiology department. The angiography of the coronary arteries showed no stenosis. In the ventriculography, there was a severe dysfunction and dilatation of the left ventricle (ejection fraction 20 %). The motility was maintained in the basal part of the left ventricle. Echocardiographically, a severe systolic dysfunction with ejection fraction 20-25 % with diffuse hypokinesis and preserved motility in the basal part was observed, with normal function of the right ventricle. The patient was referred to the anesthesia and intensive care department with provisional diagnosis of dilated cardiomyopathy.

Further course was characterized by continuous congestive heart failure, complicated by respiratory insufficiency without possibility of successful weaning. After seven days, the circulatory and respiratory parameters have worsened because of developing bronchopneumonia and sepsis despite intensive antibiotic treatment. *Klebsiella pneumoniae* was proved in the sputum microbiologically. In the terminal stage of the patient's disease, increased white blood cells count (17.1 x10^9/l, reference range 4.0-10.0) occurred, followed by elevation of plasmatic urea (40.6 mmol/l, RR 2.0-6.7) and creatinine (278 µmol/l, RR 46-90) and decreased saturation (91%, RR 94-98) despite continuous oxygen therapy. Twelve days after the initial presentation, the progression of heart and respiratory failure despite inotropic treatment lead to the patient's death. Because of unknown underlying disease, a pathological-anatomical autopsy was performed.

During the autopsy, an increased weight of the heart (490g) and increased thickness of the left ventricular wall (20mm) were remarkable. The left ventricular myocardium showed disperse brownish yellowish and whitish spots, with subendocardial accentuation (Fig. 1). Both ventricles were dilated. Valves and endothelium of the coronary arteries were smooth without thickening. In the aorta and other large arteries, no significant atherosclerosis was noticed. Both lungs were edematous weighing 980g and 550g, respectively. The lung tissue was boggy on cut section. The bronchi were filled with foamy edema fluid. The liver and spleen were slightly enlarged with a weight of 1935g and 300g, respectively; with dark red color. Apart from the heart pathology and signs of congestive heart failure, there was no significant finding in the other organs.

Histologically, the main finding was present in the myocardium. Multiple foci of necrosis were apparent in both left and right ventricles. In the subendocardial and middle layer of the myocardium, the necrotic lesions were surrounded with lymphocytic and histiocytic rim containing giant multinuclear cells, without formation of granulomas. In the centre of the lesions, necrotic myocardial cells with hypereosinophilic and partly basophilic cytoplasm were present (Fig. 2). CD68 positive immunohistochemistry proved histiocytic nature of the giant cells (Fig. 3). Desmin was positive only in vital myocardium, the inflammatory cells and necrotic debris were negative (Fig. 4). Staining for CD3, CD4 and CD8 showed disperse presence of T-lymphocytes in the necroses (Fig. 5), with slight CD4+ predominance (Fig. 6). Von Kossa stain was negative in the necrotic foci, even in repeated staining. No microorganisms were found in PAS stain and Ziehl-Neelsen stain. In the subepicardial region, foci of recent myocardial necrosis without significant inflammatory cellulisation were found (Fig. 7). Moreover, foci of scarring and hypertrophy of the adjacent myocardium were apparent, predominantly in both anterior and posterior papillary muscles (Fig. 8). Negative Congo red stain excluded myocardial amyloidosis. The samples from both left and right atrium including appendages were free of lesions described above. The mitral valve was free of any significant pathological finding. Histological examination of both lungs revealed an acute alveolar edema. In the left lung, numerous neutrophilic granulocytes were present in the alveoli, consequent with the diagnosis of purulent bronchopneumonia. Histology of the liver and spleen showed hallmarks of congestion.

Based on the finding in the heart, a diagnosis of giant cell myocarditis was rendered as an underlying disease. The other organs showed hallmarks of acute congestive heart failure, which was stated as the cause of the patient's death.

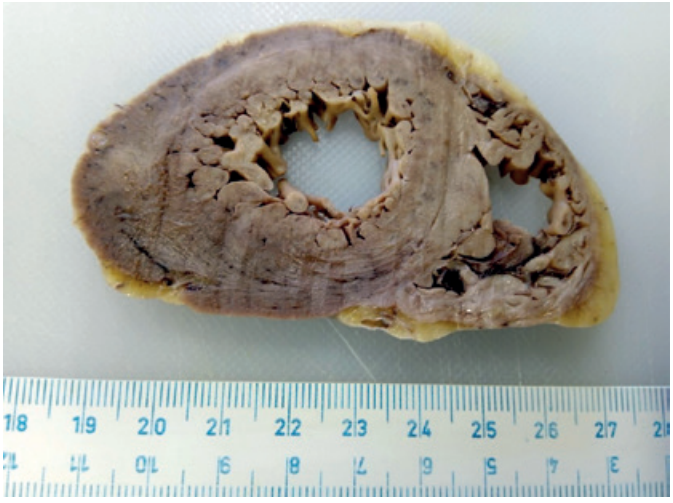

Fig. 1. Gross photograph showing the cross section of the heart with left ventricular hypertrophy and multiple small yellowish, brownish and whitish spots in the trabecular myocardium in both ventricles.

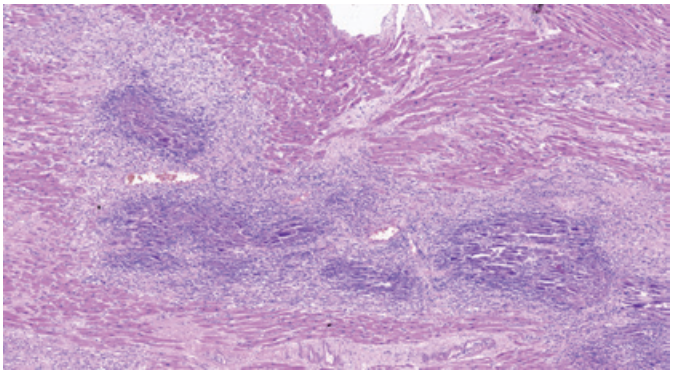

Fig. 2. Histology of the left ventricular subendocardial myocardium; note the partly confluent areas of necrosis with dense inflammatory infiltration in the periphery of the lesions. HE, magnification 6.5x.

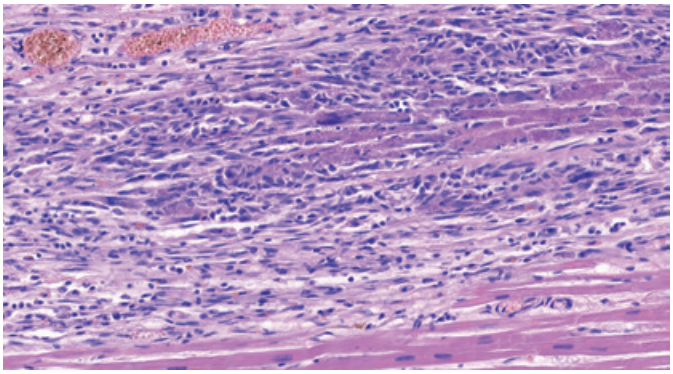

Fig. 3. Detail of the necrotic focus and inflammatory infiltrate containing multinucleated giant cells. HE, magnification 36.5x.

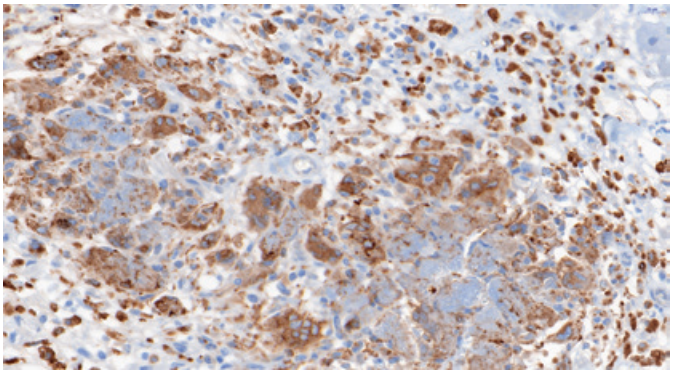

Fig. 4. CD68 immunohistochemistry documenting histiocytic nature of abundant multinucleated giant cells, magnification 53.6x.

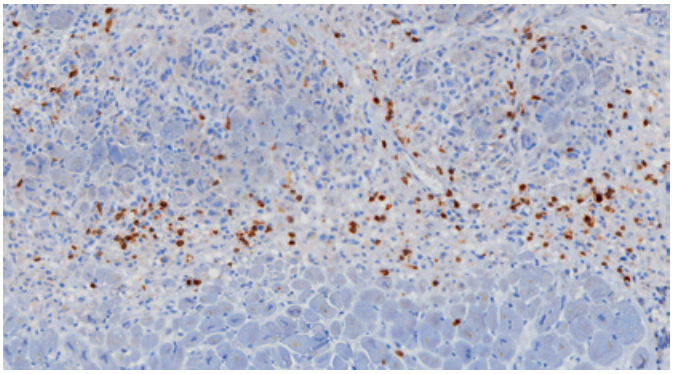

Fig. 5. CD3 immunohistochemistry showing number of disperse small T-lymphocytes in the necrotic myocardium. Histiocytes and cardiomyocytes are negative, magnification 30.9x.

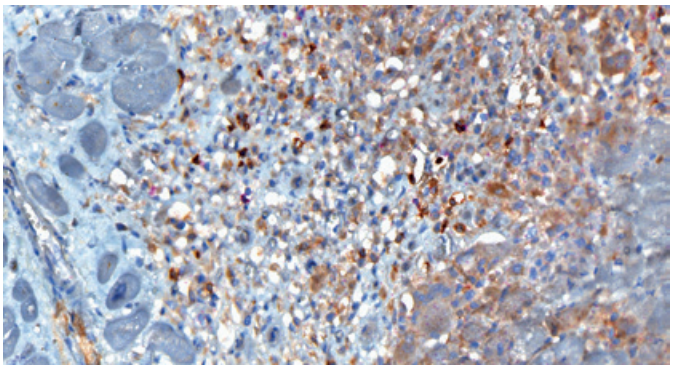

Fig. 6. Dual CD4 (brown) / CD8 (red) immunohistochemistry showing weak CD4+ in the histiocytes and giant cells, strong CD4+ in the T-cells, slightly prevailing over CD8+ (red) cells. Cardiomyocytes (left) are negative, magnification 50.4x.

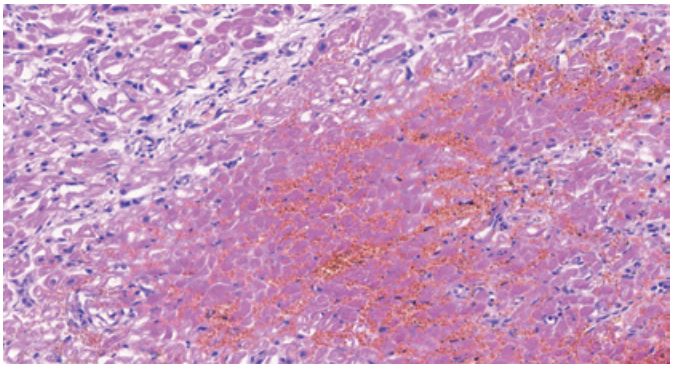

Fig. 7. Recent coagulative myocardial necrosis with hypereosinophilic cytoplasm and loss of nuclear staining, without significant inflammation. HE, magnification 31.4x.

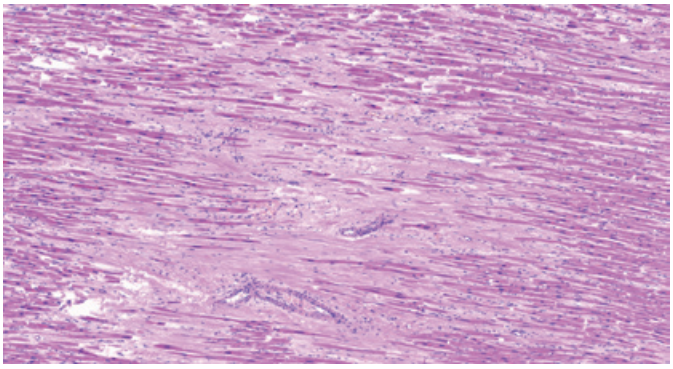

Fig. 8. Fibrous scar in the left ventricular wall. HE, magnification 10.2x

DISCUSSION

As already mentioned, GCM often affects young or middle-aged persons and manifests as a rapid heart failure, as did in our case. Approximately 20% of GCMs are associated with chronic diseases, either autoimmune or malignant, e.g. inflammatory bowel disease, rheumatoid arthritis, lymphoma, cryofibrinogenemia, myasthenia gravis, thymoma, granulomatous polyangiitis, hyperthyroidism, hypothyroidism, various infections, and drug hypersensitivity (1,6-8). Prognosis is generally poor and diagnosis is often rendered at the autopsy histology. Clinical suspicion of myocarditis often follows an ultrasound proof of left ventricular or bilateral systolic dysfunction along with normal radiological finding on the coronary arteries. Pathophysiology of GCM is not fully understood, there is evidence suggesting the pivotal role of dysregulated T-lymphocytes mediating autoimmune inflammatory response. Experimentally, GCM was induced by autologous cardiac myosin inoculation in mice (9). Upregulation of T-cell activation genes was described in patients with GCM (10). Histopathologically, abundant T-cells may be found in the lesions. The patients with GCM generally benefit from combined immunosuppressive treatment including cyclosporine (7); this fact may corroborate the theory about T-cell mediated reaction in GCM. Furthermore, there are references describing association of GCM with drug hypersensitivity (11), infection with parvovirus B19 (12) or coxsackie B2 virus (13).

GCM needs to be diagnosed histopathologically; the diagnosis is mostly based on endomyocardial biopsy, autopsy or assessment of the explanted heart, less commonly via examination of apical wedge sections removed at the time of ventricular assist device placement (3). Gross finding at the autopsy is nonspecific – the heart is usually enlarged weighing usually more than 400g. On the cut section, biventricular hypertrophy with accompanying dilatation, yellowish and scarring foci in the myocardium are apparent (8,14). Due to preferential subendocardial location of the lesions, endomyocardial biopsy from the right ventricle displays sensitivity between 68% and 80% (7,15). False negative biopsy finding may result from patchy distribution of GCM, prior therapy or insufficient sampling (5).

Our case displayed typical histomorphological features of GCM, described in the literature as chronic inflammation with prominent multinucleated CD68-positive giant cells, with obvious cardiomyocyte degeneration and necrosis without granulomas. Occasional eosinophils are described as a minor sign of GCM; these were absent in our case. Later stages show extensive fibrosis and sparse inflammation (16). In our case, lesions of various ages were present: recent lesions with abundant inflammatory cells (Fig. 2), at the same time, parts with extensive scarring

were found (Fig. 6). Interestingly, foci of recent necrosis without significant inflammatory cell presence were present in the subepicardial region (Fig. 5). From our point of view, these recent necrotic lesions were not etiologically linked to the GCM. In line with the literature, we suppose the leading role of the T-lymphocytes in pathogenesis of GCM, as we proved their presence by immunohistochemistry, documenting CD4+ slightly prevailing over CD8+ cells (Fig. 6). This finding is concordant with theory describing activating role of T helper cells in GCM (17), since these are constantly CD4+.

We hypothesise that the T-cells must be present in fresh GCM lesions. In other words, the pathophysiology of inflammatory cells in GCM differs from simple coagulative necrosis, i.e. in myocardial infarction. In simple infarction, the cardiomyocytes with hypereosinophilic cytoplasm and loss of nuclear staining are present at the beginning but inflammatory cells occur with time. In the case of GCM, we suppose that inflammatory cells are the promoting factor, whilst the necrosis occurs later. The necrotic foci without inflammation in our case may be easily explained by cardiogenic shock developing due to severe heart failure, which may lead to myocardial hypoxia even with healthy coronary vessels.

Histopathological differential diagnosis of GCM includes sarcoidosis, eosinophilic myocarditis, infectious (bacterial or fungal) myocarditis and acute rheumatic carditis (16); recently described entities which may resemble GCM are calcifying GCM and atrial GCM.

In case of sarcoidosis, the clinical finding including syncopes and heart block could be similar as in GCM in some cases. The clinical presentation of sarcoidosis is usually slow in contrast to the rapid course of GCM. Sarcoidosis is additionally characterized by lymphadenopathy (especially thoracic), hypercalcemia, and elevated serum angiotensin-converting enzyme (1). Histopathological examination of sarcoidosis shows small epithelioid granulomas with multinucleated giant cells, but there is little or no cardiomyocyte necrosis in sarcoidosis. Moreover, more extensive fibrosis may be present. In sarcoidosis, the zone of inflammation is usually more discrete with a well circumscribed border. However, in some cases of sarcoidosis, only multinucleated giant cells without clear cut granulomas may be found in the myocardium; in these cases, the proper diagnosis is difficult and relies on adequate clinical-pathological correlation.

Eosinophilic myocarditis may occur with mild intensity and minimal myocardial damage, usually as hypersensitivity myocarditis induced by drugs (antibiotics, diuretic) (18-21). Dense eosinophilic infiltration and extensive cardiomyocyte damage characterize necrotizing eosinophilic myocarditis, occurring mostly in association with primary hypereosinophilic syndrome or drug induced systemic eosinophilia. Necrotizing eosinophilic myocarditis may coexist with endocardial involvement as Löffler endomyocarditis (18,22,23). Giant cells are usually rare in eosinophilic myocarditis but may be prominent in fulminant cases (16).

Bacterial myocarditis usually follows as a complication of infective endocarditis; it is characterized by abundant neutrophils, often with microabscess formation. Granulomas with caseation necrosis may occur in tuberculous myocarditis, which is exceedingly rare. Fungal myocarditis may affect immunocompromised persons and often presents with granulomas of foreign body type which may resemble GCM. Silver stain may be useful to highlight fungal microorganisms.

Rheumatic carditis may occur in young people and may present as a heart failure like GCM. However, rheumatic disease often includes affection of pericardium and valves, most commonly the mitral valve. In our case, the pericardium and mitral valve were inconspicuous. Concerning histology, rheumatic carditis is characterized by multiple small Aschoff nodules, which may resemble GCM. Aschoff nodules are composed of smudged slightly eosinophilic connective tissue; they contain multinucleated giant cells (Aschoff giant cells) and histiocytes with central bar of nuclear chromatin (Anitschkow/caterpillar cells). These lesions are mostly situated in the interventricular septum, left ventricle wall and left atrial appendage, typically perivascularly.

Moreover, there is an emerging unit labelled calcifying giant cell myocarditis described in the literature (24-26). We suspected this due to the basophilia of the necrosis. However, we performed von Kossa staining in multiple slides without positivity; therefore, we can exclude this novel entity in our case.

Atrial GCM is an exceedingly rare unit described few years ago, characterized by benign clinical course, atrial dilatation, mitral/tricuspid regurgitation, atrial mural thrombus, and atrial hypokinesis in echocardiography. Histopathologically, similar lesions to classical GCM are found in the atria without ventricular involvement (27,28). Our case was devoid of atrial inflammatory changes and the clinical course was typical for the classical GCM.

In regard to clinical consideration, endomyocardial biopsy should be performed in case of suspected myocarditis with recent-onset high-risk major clinical syndromes (heart failure and/or life-threatening arrhythmias, in particular when associated with severe left ventricular dysfunction), not responding to standard optimized medical therapy in the short term (from hours to 2 weeks after admission) (29,30). The endomyocardial biopsy has value in rendering a diagnosis of myocarditis using Dallas criteria (18,31), with possibility to detect the specific histotype of the myocarditis, eventually with proof of particular infectious agent. On the other hand, the biopsy indication is questionable in patients presenting with low-risk syndromes and responding to standard care (29). The patients with proper intravital histopathological diagnosis of GCM may benefit from administration of an immunosuppressive treatment (32,33) or heart transplantation (34,35).

PROHLÁŠENÍ

Autor práce prohlašuje, že v souvislosti s tématem, vznikem a publikací tohoto článku není ve střetu zájmů a vznik ani publikace článku nebyly podpořeny žádnou farmaceutickou firmou. Toto prohlášení se týká i všech spoluautorů.

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