Takotsubo syndrome associated with myasthenic crisis. A case report

Síndrome de takotsubo asociado a crisis miasténica. Presentación de un caso

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Key words: Myasthenia gravis, myastenic crisis, takotsubo, cardiomyopathy, broken heart.

Palabras clave: Miastenia grave, crisis miasténica, takotsubo, cardiomiopatía, corazón roto.

** ABSTRACT **

Introduction: The takotsubo syndrome is a rare clinical entity commonly associated with elderly women (ratio 6:1), easily confused with an acute ischemic syndrome, strangely associated with a myasthenic crisis. It is characterized with chest pain, elevated biomarkers, ST segment elevation, absence of coronary flow obstruction, and a characteristic deformity (anteroapical dyskinesia) of the left ventricle; these changes associated with a stressor. Case report: A woman of 69 years, diagnosed with myasthenia gravis six years ago, who entered in the intensive care unit with a suspected diagnosis of acute coronary syndrome and respiratory failure which required mechanical ventilation. Coronary angiography discarded a coronary disease. Ventriculography revealed a systolic anteroapical deformation. Treatment was initiated with acetylcholinesterase inhibitors and plasmapheresis with partial response, it required the use of vasoactive amines, with a suitable progressive cardiovascular and neurological outcome, with echocardiographic resolution. Conclusions: The takotsubo syndrome can be associated with myasthenia gravis and myasthenic crisis. The prognosis depends on early diagnosis, appropriate differential diagnosis, immediate treatment of myasthenic crisis, and management of the hemodynamic consequences of the takotsubo syndrome.

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** INTRODUCTION **

The takotsubo syndrome (TKS), takotsubo cardiomyopathy, stress cardiomyopathy, or broken heart syndrome; is a rare disease in Mexico, poorly documented in our country, in the first instance confused with acute coronary syndrome. It is necessary to make immediate distinction based on the differential diagnosis because their medical management is largely different of an acute myocardial infarction. The pathognomonic feature of TKS is the reversible systolic left ventricular deformation as a result of anteropapical dyskinesia or hypokinesia.
coupled with compensatory hyperkinesis of the basal segments of the ventricle. The TKS is more prevalent in women (6:1) middle-aged and older, and its onset before 50 years old is exceptional. Concerning on the myasthenia gravis on the adult, in most cases it is an acquired autoimmune disorder, caused by the formation of antibodies against acetylcholine receptors, tyrosine muscle specific kinase (Musk), or LRP4. Clinically, myasthenia gravis is characterized by focal or generalized muscle weakness exacerbated induced by exercise. In some cases, myasthenia gravis may show a sudden clinical deterioration (myasthenic crisis), if the respiratory muscles are involved it can be caused an acute respiratory failure requiring mechanical ventilatory support. A myasthenic crisis is usually a critical event triggered by physical or emotional stress. Recently, it has shown that such stress reaction can even cause TKS, the joint presentation of these diseases has been described in counted neuro-critical patients. The case reported here shows an example of TKS associated with myasthenic crisis.

CASE REPORT

Woman of 69 years old, resident of Xalapa, Veracruz; housewife, smoking and alcoholism negative. History of hypertension diagnosed 20 years ago and treated with losartan 50 mg twice a day. Myasthenia gravis diagnosed 6 years ago at the National Institute of Neurology and Neurosurgery, in outpatient follow-up in that hospital; chronic treatment with pyridostigmine 60 mg every 6 hours. She began her symptoms 45 days before the hospitalization with the presence of muscle weakness in pelvic and thoracic limbs no compromising the ambulation but difficulting her daily activities, seven days after was added progressive swallowing compromise initially for masticating and then to swallow solids progressing to liquids, the reason why he stopped her oral treatment. Twelve hours after discontinuation of oral treatment was added a rapidly progressing dyspnea to grade IV New York Heart Association (NYHA), being brought to the emergency room High Specialty Centre «Dr. Rafael Lucio», in which the diagnosis of myasthenic crisis is made and specific treatment was started with intravenous neostigmine 4 mg single dose as well as plasmapheresis during 4 daily sessions with a total of 4 plasma exchanges with 60 grams of 20% albumin each, with immediate improvement of symptoms. For the next 7 days of her hospitalization had fluctuations in muscle strength and swallowing, pyridostigmine 60 mg every 4 hours was initiated, no achieving a complete improvement of symptoms. Three days later she began with dyspnea at rest and chest pain, being admitted to the intensive care unit of the hospital. Upon arrival respiratory failure was documented so we decided to perform endotracheal intubation and mechanical ventilatory support was initiated. Electrocardiogram and cardiac biomarkers were performed, and based on them an acute coronary syndrome (ST-segment elevation myocardial infarction) is suspected, it was added in the management clopidogrel 600 mg single dose, acetylsalicylic acid 300 mg load, low molecular weight heparin, anticoagulant and atorvastatin 80 mg in single dose; coronary angiography was performed at 10 hours of pain symptoms began, reporting the study without significant coronary lesions and normal flow of all epicardial arteries and morphologic and mobility ventricular abnormalities compatible with takotsubo syndrome. Treatment was started with bisoprolol 2.5 mg every 24 hours and enalapril 5 mg every 12 hours, continuing treatment until the discharge. Orotracheal extubation was achieved within 5 days and vasoactive amines were removed 24 hours later, and being discharged 5 days later, cardiovascually stable to continue ambulatory follow-up.

Physical examination on admission: blood pressure 100/70 mmHg, heart rate 110/min, respiratory rate 28/min, temperature 36.5 °C, weight 65 kg, height 1.55 mt, body mass index 27.08 kg/m2. Alert and oriented, with superior mental functions of attention, memory, praxis, gnosis with no changes, nonassessable speech; bilateral ptosis increases with fatigue tests (elevation look at a fixed point, repeated blinking), positive sign of fallen eyelid and vertical diplopia, without meningeal signs, surface and nociceptive sensitivity preserved, muscle strength in the upper extremities 4/5 and lower 5/5, muscle stretch reflexes ++ / ++++ distal
and proximal, without relaxation of sphincters, march nonassessable. Pupils with normal and symmetrical movements and reflexes, normal fundus, hydrated oral mucosa; neck without jugular ingurgitation, without lymphadenopathy. Normal and symmetrical chest movements, normal breath sounds, normal voice transmission and vocal vibrations; rhythmic heart sounds with diminished intensity and frequency, bright S1, S2 with physiological splitting, no audible S3, S4 or murmurs. Abdomen flat, soft and depressible, normal peristalsis without organ enlargement, tympanic to percussion. Lower extremities without edema, immediate capillary refill, peripheral pulses were present and normal.

Results of laboratory studies: hemoglobin 17.5 g/dL, hematocrit 52.2%, neutrophils 8,350/mm3, lymphocytes 840/mm3, monocytes 50/mm3, glucose 122 mg/dL, creatinine 0.77 mg/dL, urea 32.1 mg/dL, sodium 146 mmol/L, chloride 116 mmol/L, calcium 8.9 mg/dL, total bilirubin 1.2 mg/dL, AST 32 U/L, ALT 15 U/L, TSH 1.71 µg/dL, T4 7.38 µg/dL, T3 total 0.47 µg/IU. Urine metanephrine 0.63 mg/day, normetanephrine 498 nmol/day, dopamine 982 µg/day, noradrenaline 36 µg/day. Plasmatic catecholamines: noradrenaline 832 ng/mL, adrenaline 316 ng/mL. Biomarkers curve: troponin I: 0.67/0.59/0.29/0.06 µg/L, CK-Mb: 72/63/32/23 U/L. Electrocardiogram: sinus rhythm with heart rate of 100 beats per minute, ST segment elevation of 0.2 mV in DII, DIII, aVF and V4-V6, suggestive of inferolateral acute ST segment elevation myocardial infarction (A). Electrocardiographic monitoring after 48 hours with presence of deep T wave inversion and asymmetric branches in DII, DIII, aVF and V3-V6 (B).

Figure 1. A 12-lead electrocardiogram in sinus rhythm with heart rate of 100 beats per minute, ST segment elevation of 0.2 mV in DII, DIII, aVF and V4-V6, suggestive of inferolateral acute ST segment elevation myocardial infarction (A). Electrocardiographic monitoring after 48 hours with presence of deep T wave inversion and asymmetric branches in DII, DIII, aVF and V3-V6 (B).

Figure 2.

Chest X-ray in anteroposterior projection with increased bilateral vascular pattern, without apparent cardiomegaly, no other visible changes.

Coronary angiogram: selective femoral system with 6 French (Fr) JL and JR catheters, observed: left main coronary system bifurcated, anterior descending artery Gensini type III, without significant lesions, and TIMI III distal flow. Circumflex without significant lesions, normal distal flow. Right coronary artery dominant, without significant coronary lesions, normal distal flow (Figure 3). Ventriculography observed basal hyperkinesis with anteroapical and inferoapical hypokinesia (Figure 4). Echo-
cardiogram: transthoracic study after 3 months of follow-up, with left ventricle of normal size, without alteration in partial or segmental mobility, ejection fraction of 76%, without valvular disease, systolic pressure in the pulmonary artery 22 mmHg, the rest with no alterations (Figure 5).

DISCUSSION

The TSK is a clinical entity described in 1990 by Sato, et al; who described the first cases characterized by acute anginal chest pain in the absence of angiographic coronary obstruction and apical systolic heart characteristic deformation. The TKS owes its name to the Japanese technique of fishing for octopus (tako: octopus, tsubo: pot) in pots, whose forms recall the left ventricle in systole during the acute phase of the syndrome. The TKS as a clinical entity was considered in 2001, with the study of Tsuchihashi, et al; who published a retrospective analysis of 88 patients with a syndrome characterized by chest pain, initially identical electrocardiographic changes of acute myocardial infarction, elevated cardiac biomarkers, coronary arteries without significant lesions and characteristic apical left ventricular dyskinesia/hypokinesia, that normalize within a few days. In subsequent years new cases have been reported in different countries, thus proving that the TSK is not restricted to certain geographical areas.

It mainly affects elderly women (over 80% of cases). Its pathogenesis is not yet purely determined and is probably multifactorial. Theoretically the acute and intense adrenergic hyperactivity which is due to physical, psychological or both stress, increase serum levels of catecholamines, such sympathetic hyperactivity causes a depression of the contractile function of the left ventricle in the apical region by focused microvascular spasm (neuromyocardic syndrome), with the consequence of morphological cardiac deformation, characteristic of TSK. As observed in the series of Tsuchihashi and in our patient, the TSK was preceded by a stressful event, which supports the hypothesis proposed above; however, there is still no evidence of elevated catecholamines in the myocardium of these patients.

In the original series of Tsuchihashi, only 7% of cases had a neurological factor as a possible trigger, none of the patients reported or associated with myasthenia gravis. In recent years there have been reports of TKS related with myasthenic crisis and other neurological processes such as: subarachnoid hemorrhage, stroke, Guillain-Barré syndrome and convulsive crisis. In all of them the stress is related as a trigger.

Counting our case, there have been reported a total of eleven cases of TKS in patients with myasthenic crisis. Their characteristics...
are summarized in table I. In two of them can be attributed a potential responsible role to the plasmapheresis.\textsuperscript{19,20} Although the limited temporal relationship between the development of TKS and myasthenic crisis in the absence of another therapeutic factor, allows us to provide a greater weight in terms of causality to the stress. Another consideration may be generated from the fact that there is no published case of TKS as an adverse effect of treatment with plasmapheresis.

Including our patient, in ten patients the TKS was presented during the mechanical ventilation support (Table I). In a patient the orotracheal intubation after a seizure during myasthenic crisis was necessary. Ten patients received acetylcholinesterase inhibitors during acute event of TKS, six patients received steroids, two required mycophenolate mofetil, one tacrolimus, three patients were treated with immunoglobulin and four patients with plasmapheresis. Ten patients developed classical TKS with apical dyskinesia and basal segments hyperkinesia, and one patient developed a global TKS with akinesia/hypokinesia of all segments. Four patients received dobutamine, one disopyramide, two diuretics, one lidocaine and two noradrenaline. Nine patients recovered completely of TKS, but in two patients the outcome was fatal, one of the deceased patients developed global type. Only one of the patients had a recurrence of TKS.

A direct pathophysiological association between myasthenic crisis and the TKS is unlikely because in myasthenia gravis the cholinergic deficit occurs in the receptor of the striated skeletal muscle, and the pathophysiological feature more accepted in the secondary TKS to any cause is the hyperadrenergic systemical state, usually mediated by physical or emotional stress.

The stress due to myasthenic crisis can be attributed to respiratory failure and anxiety caused by transient dyspnea. Probably the inducing factor of myasthenic crisis, lead to physical stress and contribute to the development of TKS.

**CONCLUSIONS**

The TKS must be taken into consideration as a clinical entity without direct pathophysiological relationship with myasthenia gravis and myasthenic crisis. Although the association is rare, it is not known for sure their relationship in clinical practice because of the few existing case reports. The prognosis for these patients, as observed in our clinical case, depends on timely diagnosis, appropriate differential diagnosis, immediate treatment of myasthenic crisis, and with the management of hemodynamic consequences of TKS. The cardiologist needs to know that there may be a correlation between the two

![Figure 5. Transthoracic echocardiogram of three months after discharge, in 4-chamber axis projection, the left ventricle shows no alterations in morphology during relaxation (A), without chamber enlargement, left ventricular ejection fraction preserved displayed by Teichholz (B), and adequate ventricular mobility by M mode (C).](image-url)
diseases, and it is the duty of neurologist to know the existence of this cardiomyopathy and take it into consideration in all patients with myasthenic crisis and other neurocritical conditions also related.

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REFERENCES


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