

Methotrexate a cause of myocarditis, Myth or reality?

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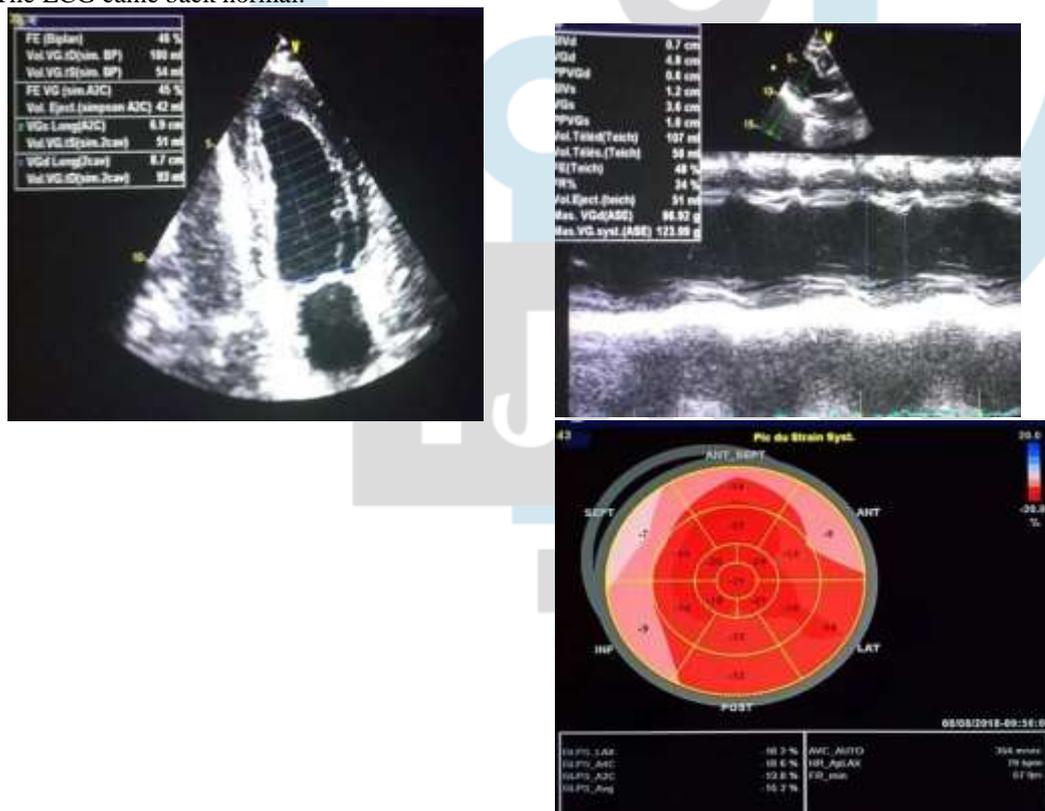
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Introduction:

Myocarditis is an inflammation of the myocardium, with on histological examination an infiltrate of inflammatory cells and signs of myocyte necrosis, the diagnosis of acute myocarditis must be considered in the presence of signs of heart failure in the absence of coronary or valvular disease. Acute and subacute myocarditis are most often of infectious origin, viral, they can also be linked to parasitosis, to the intake of toxic substances, in particular the case of immunosuppressive treatments and during autoimmune pathologies. Their clinical expression and prognosis are highly variable, making their diagnosis and treatment difficult. The current incidence of the disease is, moreover, also difficult to establish because the diagnosis of certainty depends, in the state, on the realization of myocardial biopsies and these are not systematically carried out, nor even justified. When the clinical presentation does not include any signs of severity, the disease is generally self-limiting without specific treatment. However, the condition can also present as cardiogenic shock or sudden death. The etiology of myocarditis has a predictive prognostic value and directs, in certain cases, towards a specific treatment.

Observation:

We report the observation of Mr. GM, 56 years old, type II diabetic under ADO for 04 years, followed for rheumatoid arthritis since 2002 under corticosteroid therapy and novocine then under corticosteroid therapy alone admitted to the rheumatology department for spinal pain related to fractures vertebral tiered. The patient was put on immunosuppressive treatment based on methotrexate, fifteen days later, he presented edema of the lower limbs without other associated signs. Liver and kidney function tests were normal. The ECG came back normal.



Figures 1,2,3: TTE ascending an undilated LV seat of global hypokinesia with EF at 46%

The TTE showed: accentuated global hypokinesia in the lower part with an EF of 40% with no significant valve disease.

The cardiac MRI objectified the presence of a non-dilated LV seat of segmental kinetics disorders with moderate alteration of systolic function FE at 40% and focus of late intramyocardial enhancement corresponding to sequelae of myocarditis. As part of the etiological assessment, the biological assessment returned to normal, the infectious and toxic assessment was negative, and

the absence of another systemic disease.

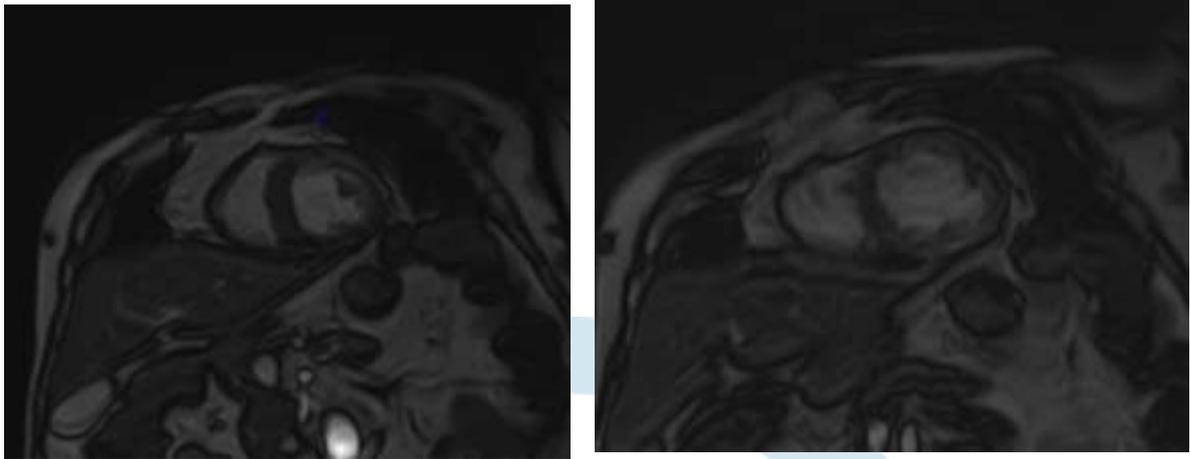


Figure 4.5: Cardiac MRI with appearance of late intramyocardial enhancement.

The patient was put on diuretic treatment at the beginning then on ACE and beta-blocker at the optimal dose and he evolved well with disappearance of congestive signs after three days of diuretic treatment.

Discussion:

Methotrexate is an antimetabolite used as an anticancer treatment and in the treatment of systemic diseases, it inhibits dihydrofolate reductase, a key enzyme in the metabolism of folic acid. Methotrexate has long been characterized by its toxicity for rapidly proliferating cells, in particular hematopoietic lineages, and skin cells (1); it may be the cause of acute myocarditis in less than 1% of patients. The family of anti-metabolites, to which methotrexate belongs, can be responsible for cardiotoxicity such as myocarditis (2), rhythm disorders and even coronary syndromes through spastic phenomena and direct actions on the coronary endothelium. The pathogenesis of cardiomyopathy secondary to chemotherapy is still poorly understood, several mechanisms have been described and classified into two subtypes: Type 1 follows structural and usually dose-dependent myocardial damage. It is attributed to myocyte damage secondary to the production of free oxygen radicals responsible for increased oxidative stress (3). Other mechanisms have been suggested, such as direct apoptosis of myocardial cells, transcriptional changes in myocyte ATP production, repression of sarcoplasmic reticulum calcium-ATPase messenger RNA expression (4). leading to a decrease in contractility or a prolonged decrease in glutathione peroxidase activity and an alteration of the respiratory chain secondary to mitochondrial DNA lesions. The course is rarely reversible, resulting in a decline in left ventricular function that can lead to heart failure of varying severity (5). Type 2 is characterized by myocardial dysfunction mainly described with the new targeted therapies. Unlike type 1, this form is usually reversible and independent of the dose. Endomyocardial biopsy analysis usually does not reveal structural damage (6). This damage would be linked to a phenomenon of hibernation or myocardial stupefaction. In this reported case, the cause-and-effect relationship involving methotrexate as etiology of myocarditis cannot be affirmed, several causes can be evoked the occurrence of the pathology within the framework of its systemic disease, it is autoimmune myocarditis (7). But the chronology of the events in particular the appearance of the symptoms following the introduction of methotrexate is not in favor of the immunological track (8). Like any immunosuppressant, methotrexate can promote a new infection or aggravate symptoms during viral infection (9), for example, sometimes justifying stopping treatment after considering the risk-benefit ratio. The infectious anamnesis not reporting signs in favor of a viral infection is an argument against (10). Finally, the toxic cause is probably the most retained in this context, given the rapid improvement after stopping methotrexate. The confirmation of an etiology would have required the realization of

biopsies not made considering the clinical improvement of our patient under symptomatic treatment (11). This observation is a reminder of the potential seriousness of the adverse cardiac effects of immunosuppressants, hence the obligation to respect their prescription methods and protocols and their close monitoring.

In conclusion:

Acute heart failure, in the absence of known valvular or coronary disease, in a patient on immunosuppressants should suggest acute myocarditis, which conditions the discontinuation of immunosuppressive treatment and the search for alternatives.

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