Recurrent myocarditis revealing a desmoplakin cardiomyopathy successfully treated with anakinra

Sirs,

Myocarditis is an inflammatory condition of the myocardium that can extend to the cardiac conduction system and pericardial layers. Approximately 25% of patients eventually develop complications including left ventricular systolic dysfunction, ventricular arrhythmias, or acute heart failure (1). Viral infections represent the main cause of myocarditis, followed by autoimmune disorders which explain 7% of the cases (2). While these inflammatory triggers are well established, a comparable proportion of myocarditis cases marks the onset of dilated or arrhythmogenic cardiomyopathies, an association often overlooked in clinical practice (3). Here, we report the case of a patient with recurrent myocarditis revealing a pathogenic desmoplakin (DSP) variant and successfully treated with IL-1ß receptor antagonist, anakinra.

Our patient was an 18-year-old male athlete, who initially presented to the emergency room with features of acute myocarditis, evident from clinical manifestations, elevated troponins (5000 ng/L, N<50) and characteristic MRI findings (Fig. 1). Initial investigations, including autoimmune and microbiological laboratory tests, were negative. Treatment with ACE inhibitors, beta-blockers, colchicine, and aspirin was initiated, and rest was advised. However, he experienced recurrent episodes at 12 and 16 months, prompting referral to our department. The patient had no significant medical or family history except that his father died suddenly without any known related illness. Our patient had no extra-cardiac manifestations so far. Cardiac MRI was performed and revealed new T2 hypersignals and sequelae from previous episodes. Endomyocardial biopsies showed no granuloma, or giant cells. Given the recurrent episodes of myocarditis, the absence of an identifiable trigger, and the family history of sudden death, a genetic cardiomyopathy was suspected. Genetic screening ultimately identified a pathogenic DSP variant (c.3337C>T) leading to a truncated protein (p.R1113*) and responsible for a DSP-related cardiomyopathy. Treatments with colchicine, glucocorticoids, and methotrexate were attempted to target myocardial inflammation but the patient experienced two additional flare-ups within three months. Notably, switching to anakinra, an IL-1β receptor antagonist, led to the complete prevention of flares over a five-year period without any adverse effects so far.

DSP is a desmosomal binding protein critical for normal force transmission in the myocardium (4). Pathogenic variants in the DSP gene cause a unique form of arrhythmogenic cardiomyopathy characterised by intermittent inflammatory episodes of myocardial injury, clinically similar to myocarditis, left ventricular fibrosis leading to systolic dysfunction and a high incidence of ventricular arrhythmias (5, 6). A recent comprehensive study of 800 patients with DSP pathogenic variants demonstrated that the recurrence of myocarditis-like episodes is correlated with worse outcomes (7). To date, no therapeutic intervention has proven efficient to halt the disease.

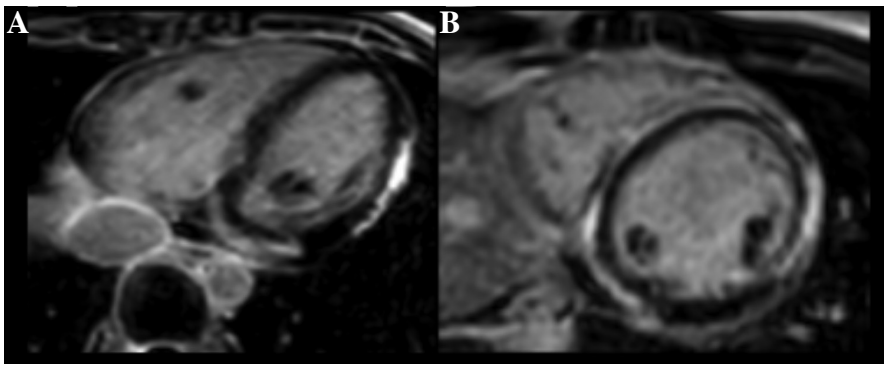

Fig. 1. Extended subepicardial late gadolinium enhancement along the lateral (**A**) and inferior (**B**) cardiac walls.

Clinical observations in combination with recent laboratory data highlighted that innate immune activation is involved in DSP-related myocardial injury (8). Using organoid system, Selgrade *et al*. demonstrated that $DSP^{-/-}$ engineered heart tissues (EHTs) exhibited a transcriptomic signature of immune activation (*e.g*. NF-κB), an excessive response to TLR agonists, mirrored by inflammatory cytokine release (*e.g*. IL-1β, IL-6) which are responsible for a negative effect on contractility as compared with $DSP^{+/+}$ EHTs (8). Interestingly, genetic correction of $DSP^{-/-}$ EHTs only partly corrected the NF-κB pro-inflammatory mediators, suggesting the contribution of non-DSP-induced inflammatory cytokines. Colchicine treatment reversed contractile defects in the organoid model (8). In our patient, colchicine was not sufficient in preventing recurrence of myocarditis-like episodes. The $DSP^{-/-}$ EHT model does not allow to recapitulate the complete pathophysiology of DSP-related cardiomyopathy, especially the role of tissue-resident lymphocytes and macrophages (8). We could postulate that colchicine may not be sufficient to abolish inflammation once the myocardium is infiltrated by immune cells.

Correlation between episodes of myocardial injury and adverse outcomes suggests that preventing these myocarditis-like events through targeting inflammation could improve long-term prognosis in DSP-related cardiomyopathy patients (7). Prospective studies are needed to confirm the effectiveness of this approach. Our single clinical experience, bolstered by recent laboratory findings, suggests that a deeper understanding of the connections between innate immunity and DSP cardiomyopathy may pave the way for timely treatments and prevent long-term complications. These findings may also be expanded to other genetic cardiomyopathies associated with sustained innate immune activation.

With this observation, we hope to raise awareness among clinicians that genetic conditions may be revealed by recurrent myocarditis and that IL-1ß blockade can be an efficient therapy.

Acknowledgements

We would like to thank Dr Delphine Gamondes for providing us with the cardiac MR images.

T. Barba, *MD, PhD*
M. Robert, *MD*
A. Hot, *MD, PhD*

Department of Internal Medicine, Edouard Herriot Hospital, Lyon University Hospital, Lyon, France.

Please address correspondence to:
Thomas Barba,
Department of Internal Medicine,
5 Place d'Arsonval,
69003 Lyon, France.
E-mail: thomas.barba@chu-lyon.fr

Competing interests: none declared.

References

1. AMMIRATI E, MOSLEHI JJ: Diagnosis and treatment of acute myocarditis: a review. *JAMA* 2023; 329(13):1098-113. https://doi.org/10.1001/jama.2023.3371
2. AMMIRATI E, CIPRIANI M, MORO C *et al*.: Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: Multicenter Lombardy Registry. *Circulation* 2018; 138(11): 1088-99. https://doi.org/10.1161/circulationaha.118.035319
3. LOTA AS, HAZEBROEK MR, THEOTOKIS P *et al*.: Genetic architecture of acute myocarditis and the overlap with inherited cardiomyopathy. *Circulation* 2022; 146(15): 1123-34. https://doi.org/10.1161/circulationaha.121.058457
4. SMITH EA, FUCHS E: Defining the interactions between intermediate filaments and desmosomes. *J Cell Biol* 1998; 141(5): 1229-41. https://doi.org/10.1083/jcb.141.5.1229
5. SMITH ED, LAKDAWALA NK, PAPOUTSIDAKIS N *et al*.: Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2020; 141(23): 1872-84. https://doi.org/10.1161/circulationaha.119.044934
6. AMMIRATI E, RAIMONDI F, PIRIOU N *et al*.: Acute myocarditis associated with desmosomal gene variants. *JACC Heart Fail* 2022; 10(10): 714-27. https://doi.org/10.1016/j.jchf.2022.06.013
7. GASPERETTI A, CARRICK RT, PROTONOTARIOS A et al.: Clinical features and outcomes in carriers of pathogenic desmoplakin variants. *Eur Heart J* 2025; 46(4): 362-76. https://doi.org/10.1093/eurheartj/ehae571
8. SELGRADE DF, FULLENKAMP DE, CHYCHULA IA *et al*.: Susceptibility to innate immune activation in genetically mediated myocarditis. *J Clin Invest* 2024; 134(13). https://doi.org/10.1172/jci180254