Firenze
19-21 ottobre 2023

52° CONGRESSO NAZIONALE SICP

Meyer Health Campus

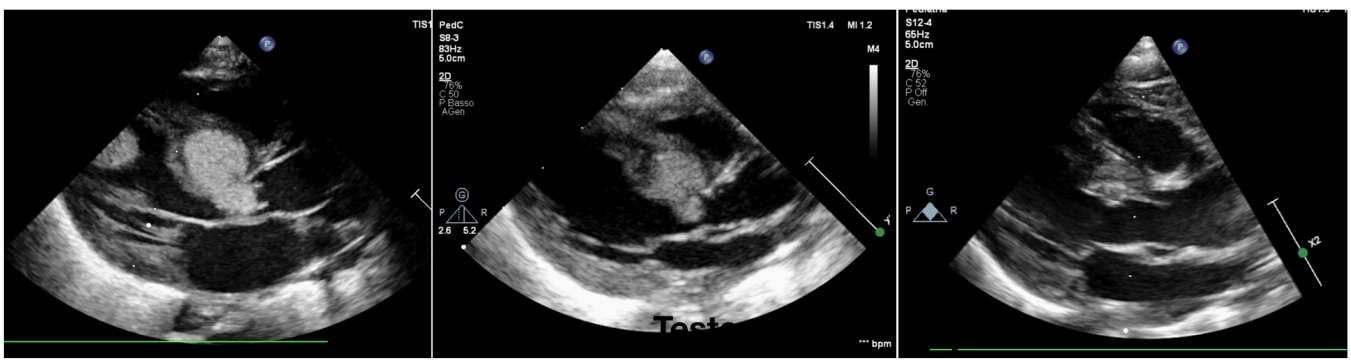
mTOR-inhibitors in tuberous sclerosis complex and multiple rhabdomyomas: a case report and management of preterm newborns

M. Pasquinucci 1, N. Falchi 1, M.E. Derchi 2, A. Siboldi 2, E. Morelli 1, C. Zannelli 3, A. Rimini 1

1 DINOGMI, University of Genova, Genova, Italy
2 Department of Cardiology, IRCCS G. Gaslini, Genova, Italy
3 Department of Cardiology, San Martino General Hospital, Genova, Italy

INTRODUCTION

Tuberous sclerosis (TSC) is a multisystem disease caused by mutations in the TSC1/2 genes leading to the overactivation of mTOR with consequent dysregulation of cellular apoptosis; hamartomas can be found in kidneys, optic nerves, CNS, lungs, skin; in 60% of TSC, cardiac rabdomyhomas can be found and may cause left ventricular outflow obstruction, contractility alterations, arrhythmias and sudden death. Rabdomyhomas can undergo spontaneous regression. Otherwise, they can be submitted to surgery; mTOR-inhibitors such as everolimus and sirolimus have been shown to cause a significant reduction of tuberous lesions.



1a: first day of hospital stay. 1b: 7 days after starting mTOR-inh therapy. 1c: 1 month after suspension of sirolimus

CASE REPORT

We admitted a late preterm newborn with multiple cardiac neoformations consistent with rhabdomyomas. The largest was located into the intraventricular septum and one of its lobes flooded into the aortic lumen during systole compromising the transvalvular flow thus creating a relevant gradient. On day two, the little patient showed ECG findings consistent with paroxysmal endocardial tissue transitory ischemia during stress or tachicardia, therefore propranolol treatment was started. Considering that surgery was contraindicated (low weight, suboptimal vitals and clinical conditions) we decided to start therapy with rapamycin pathway inhibitors (sirolimus 0.1 mg/day, 4.5 mg/m2/week) and a progressive reduction of the rhabdomyomas followed. The largest tuberous showed a decrease of around 30% of its volume at the sixth day of mTOR-inhibitors therapy, and a decrease of 50% of its mass at the cardiac ultrasound performed on day 15. On day 16 blood tests showed neutropenia and anemia likely as side effects of the mTOR-inhibitors treatment, and a rapid deterioration of vitals and clinical conditions of the patient followed with marked abdominal distension, vomiting, diarrhea along with an increased inflammatory markers. Considering the full blown septic state, sirolimus was suspended and antibiotics were promptly started: a progressive improvement followed, as well as further reduction of rhabdomyomas.

DISCUSSION

Therapy with mTOR-inhibitors can be initiated off-label both in the newborn and in pregnant women with prenatal diagnosis of TSC of the foetus, but there is scarcity of evidences of their use on preterm newborns. A consensus that defines the timing, dosage, duration and serum target of these drugs and the standardization of their use in such patients is needed, considering the numerous findings in the literature of a positive effect on the prognosis

We have to pay greater attention with preterms, given the greater predisposition of this cohort of patients to the development of infectious and/or hematological morbidities, which can be exacerbated by the use of mTOR-inhibitors. Only two cases of preterms with multiple cardiac rhabdomyomas treated with everolimus and sirolimus have been reported, with benefit in reduction of size of the cardiac tuberous; in the first, as in our case, mTOR-inhibitors therapy caused a sepsis due to iatrogenic immunosuppression. However, even if some authors proposed the use of antibiotic prophylaxis with cotrimoxazole, it seems not to be strongly recommended as there are no evidence of its efficacy in patients treated with sirolimus. Moreover, cotrimoxazole is known to eventually cause myelosuppression such as mTOR-inhibitors themselves. In conclusion, rapamycin treatment seems to lead to a great reduction of RM volumes and associated symptoms, but further studies are needed to consider it in such a cohort of patients.