Authors' Response to the Review Comments

Manuscript No:	62623
Article Title:	Acute inferior myocardial infarction in a young man with testicular seminoma- case report
Journal Name:	World Journal of Clinical Cases
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Dear Editor,

I am pleased to resubmit for publication the revised version of manuscript no. 62623, with the title "Acute inferior myocardial infarction in a young man with testicular seminoma- case report". We appreciate the time and efforts made by the editor and reviewers in proofreading this manuscript; their feedbacks helped improve our paper and clarify essential aspects.

With reference to the comments and suggestions of reviewers and editors:

Reviewer

This is quite an interesting case report about a young man who suffered an apparent acute myocardial infarction (AMI) following chemotherapy for testicular carcinoma: treatment had included cisplatin. Coronary angiography was normal except for the presence of an apparent coronary stenosis and associated thrombosis (not directly visualized) near the crux. The study is an important reminder of the risk of ischemic events, even after chemotherapy, in such situations. While the report is interesting, the authors have missed several opportunities:

(1) What caused the apparent AMI? The lesion looks like an area of coronary vasoconstriction rather than atheroma, as best as I can guess. Was the RCA injected with NTG to see whether the "lesion" disappeared? If not, why not? Cisplatin is known to induce vascular endothelial dysfunction, perhaps mainly via impairment of nitric oxide synthase activity, but also perhaps via impairment of hydrogen sulphide availability. The authors need to incorporate some of this information into their report.

We thank the reviewer for the comments; indeed the right coronary artery was injected with nitroglycerine 200 μg and the AMI culprit lesion slightly improved, but did not disappear. The most likely explanation for the reduced response to nitroglycerine is that the lesion encountered on angiography is the result of a complex mechanism including also endothelial erosion apart of coronary vasoconstriction. Erosion of the endothelial as one main mechanism of cisplatin vascular toxicity is sustained by both experimental and clinical data supporting endothelial

damage, apoptosis as well as platelet adherence, activation and aggregation (Dieckmann et al. 2010; Ito et al. 2012). Also, an increasing body of evidence points that cisplatin also induces endothelial dysfunction, affecting both the relaxation and contractile function by a severe damage to blood vessel walls (Jiang et al. 2014). The mechanism underlying the latter is mainly reduction of eNOS and increase in plasminogen activator inhibitor 1 (Herradón et al. 2017), but also include other mechanisms such as hydrogen sulphide availability (Francescato et al. 2011). All the above information have been included between lines 201-214.

(2) Was Takotsubo excluded? I think that this is a very minor point, because the chemo agents concerned do not usually cause TTS, but for innocent readers this is a big issue. The authors should provide, at the very least, echo results.

Thank you for your remark. Indeed, Takotsubo syndrome was excluded as the patient did not have dyskinesia of left mid-ventricular segment with or without apical involvement as the Mayo clinic criteria request for diagnosis (Scantlebury and Prasad 2014), for more details we have included also videos with four and two chamber apical views in our manuscript. Furthermore, the undertaken chemotherapy of our patient is not associated with Takotsubo syndrome, but seen the unpredictability of the disease should be considered even if not reported previously with the presented chemotherapy. We have included the above comments at your suggestion in the manuscript between lines 190-197.

(3) How was treatment selected? There is actually some justification for the atorvastatin, but the beta-blocker is quite bizarre in the context of possible coronary spasm. The authors can hardly claim that the infarct was large enough to leave the patient with heart failure and/or risk of VF.

Thank you for your remark, indeed we treated our patient with non-dihydropyridinic calcium-blocker and isosorbide dinitrate on short and long-term; there was a typing mistake that we corrected at line 168. Just before angiography in the emergency department the patient received one single dose of beta-blocker as he was tachycardic, but after the direct visualization of the coronary lesion he was treated with verapamil and isosorbide dinitrate along with dual antiplatelets, anticoagulants and atorvastatin in the coronary intensive care unit and afterwards, as long-term treatment. As you mentioned there was no reason to administer a beta-blocker as long as the patients remained without heart failure symptoms and the left ventricular ejection fraction was only mildly affected.

(4) Was this the only episode of chest pain? This is an important point either way. Most patients with coronary spasm have recurrent episodes. Normal treatment would include calcium antagonists, and it is worth knowing that thrombus formation has now been implicated in the pathogenesis of coronary spasm.

This is the only episode of chest pain, pinpointed now at line 120; in the follow-up period of 6 months he did not have recurrent episodes, lighted at line 175-6. Indeed, although not frequently, solely prolonged vasospasm might induce secondary thrombus formation (Kobayashi et al. 2013), which might have been also in our case. We have included the suggested pathophysiological mechanism in the manuscript between lines 223-225.

We would like to thank the referees and editors for evaluating our manuscript. We have addressed all the reviewers' concerns in a proper way and believe that our paper has improved after revision. We look forward to hearing from you regarding our submission and would be glad to respond to any further questions and comments that you may have.

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