Answer to reviewer

Reviewer Name: Anonymous
Review Date: 2020-08-07 10:36
Specific Comments To Authors:
The case study is very detailed, thoroughly documented (8 figures and 1 table). It's only a second of its kind in the world literature. What is especially important is the practical aspect of the study - the rutine test UPCR which is a very cumbersome process of assessment of protein excretion in relation to creatinine in the daily collection of urine is replaced with with the same index determined in any random urine sample. This is documented with a high statistical compliance (figures 7 and 8). All the references are quoted in the manuscript. The descriptive style the authors chose was very original and captivating. Minor editing is required in lines 23-24 "leading to hemodialysis" should be clarified; lines 18-21 should be explained as the meaning is ambiguous.
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)

Answering:
First of all, thank you for this kindly appreciation.
About “leading to hemodialysis”:
According to contemporary evidence from literature, m-TKI, interrupting the mechanism after binding of VEGF-A and VEGFR, should majorly feature results of changing of cytoskeleton such as nephrotic syndrome. However, the role of complement activation in this type is still unclear, and thus still some sporadic cases are reported with thrombotic microangiopathy, mediated by complement activation (9. **Paschke L,** Lincke T, Mühlberg KS, Jabs WJ, Lindner TH, Paschke R. Anti VEGF-TKI Treatment and New Renal Adverse Events Not Reported in Phase III Trials. *Eur Thyroid J.* 2018;7(6):308-312. PMID: 30574461 DOI: 10.1159/000491387; 10. **Hyogo Y**, Kiyota N, Otsuki N, Goto S, Imamura Y, Chayahara N, Toyoda M, Nibu KI, Hyodo T, Hara S, Masuoka H, Kasahara T, Ito Y, Miya A, Hirokawa M, Miyauchi A, Minami H. Thrombotic Microangiopathy With Severe Proteinuria Induced by Lenvatinib for Radioactive Iodine-Refractory Papillary Thyroid Carcinoma *Case Rep Oncol.* 2018; 11(3):735-741. PMID: 30519176 DOI: 10.1159/000494080).
The worst scenario would need intervention of hemodialysis (9.**Paschke L,**

Lincke T, Mühlberg KS, Jabs WJ, Lindner TH, Paschke R. Anti VEGF-TKI Treatment and New Renal Adverse Events Not Reported in Phase III Trials. Eur Thyroid J. 2018;7(6):308-312. PMID: 30574461 DOI: 10.1159/000491387).

About "This interaction will lead to alterations in the cytoskeleton and will manifest as nephrotic syndrome or minimal change disease as nephrotoxicity. The role of complement factor H of this type still remains unclear." :

In nephrotoxicity featuring thrombotic microangiopathy is now believed to have RelA up-regulation, which will subsequently inhibit C-Maf–inducing protein (c-mip) binding to its promoter. In this point of view, if one drug interrupts the pathway after VEGF-A binds to VEGFR, it will allow c-mip accumulation and overexpression. C-mip accumulation and overexpression will further cause damage by means of cytoskeletal disorganization and the effacement of foot processes in podocyte and nephrin. (**Zhang SY**, Kamal M, Dahan K, Pawlak A, Ory V, Desvaux D, Audard V, Candelier M, BenMohamed F, Matignon M, Christov C, Decrouy X, Bernard V, Mangiapan G, Lang P, Guellaën G, Ronco P, Sahali D. c-mip impairs podocyte proximal signaling and induces heavy proteinuria. *Sci Signal.* 2010;3(122):ra39. PMID: 20484117 DOI: 10.1126/scisignal.2000678).
For this microscopic evidence, drugs, causing nephrotoxicity after binding of VEGF-A/VEGFR, will feature disorganization of structure, causing heavy proteinuria. However, there are still no enough evidences completely ruling out roles of complement factor H in this type of drug, and thus we could make confident conclusions that it will not have thrombotic microangiopathy in this type of drugs.