Comments to the author:

Reviewer #1:

The case report entitled Turner syndrome with primary myelofibrosis (PMF), cirrhosis and ovarian cystic mass： A case report" by Lin-wei Xu et al, describes the case of a 20-year-old woman diagnosed with Turner syndrome, primary myelofibrosis, cirrhosis, and an ovarian cystic mass. The case seems interesting but is lacking many details that would enhance the case presentation and discussion. While this is not the first case associated with cirrhosis and turner syndrome, the addition of PMF and an ovarian cyst mass is novel. This case describes an interesting combination of pathologies that make the case somewhat convoluted, but at the same time gives rise to a nice discussion, which unfortunately the manuscript does not contain.

1. Please provide a more detailed presentation of the case.

**Revision 1:** Thank you for your advice. Some of the text was ambiguous, and we have modified the text to be more clear. We have made adjustment on the part of "CASE SUMMARY" to express this case more clearly and we have added some details of "*History of present illness*" and as you suggested, we supplemented the results of "*laboratory examination*" such as "while cholesterol and glucose levels were in the normal range (Table 1). The hepatitis panel, human immunodeficiency virus test, and autoantibody screening results were negative (Table 2)" (Page 6). We also make tables to clearly show the complex examination results and add some details in the part of "TREATMENT", such as "Ruxolitinib was intermittently used based on the blood platelet count. The recommended starting dose is 5mg or 10 mg twice daily (b.i.d.), depending on platelet counts (≥ 50 to < 75 × $10^9$/L, 75 to 100 × $10^9$/L, respectively) regardless of Hb level. When the blood platelet count < 50× $10^9$/L, ruxolitinib use is recommended to cease. "(Page 8).

2. Provide a detailed laboratory data at presentation (preferably in the table format). Please be very careful with how you describe the units of each value, as it makes the case more confusing. For instance, you report the patient has a hb of 38g/dl??? You meant to say 38g/l?? or 3.8g/dl???, there is a huge difference, so please make sure this mistake is corrected. In the same regard, there is another hg value that you report using the same units. If what you described is correct, please discussed the result in the discussion section.

**Revision 2:** We really appreciate the reviewer's attention to detail, and we feel very sorry for the mistake. We have rechecked all units of each value, and corrected Hb of 38g/dl to 38g/L. As you suggested, we have used Table 1, Table 2 and Table 3 to show the results of laboratory data clearly.

We apologize again for our mistake and thank you very much for your kind.

3. What autoantibodies was she screened for? Please report the names and values.

**Revision 3:** Thank you for reminding us to perform a detailed analysis of autoantibodies. We have listed all the names and values of autoantibodies in the Table 2: Autoimmune antibody detection of the patient.

4. Was the patient screened for genetic disorders related to liver cirrhosis? For instance, was hemochromatosis ruled out? was she screened for Wilson's disease? A thorough panel of genetic disorders for cirrhosis given her existing condition should be warranted.

**Revision 4:** Thank you for your question. Your question is very important, and we have added some examinations of the patient and discussion in the article. (Page 6) shows that "liver fibrosis markers were significantly elevated (Table 3), The significantly decreased amount of ferritin, normal

ceruloplasmin and ophthalmic testing without ophthalmic signs (Kayser–Fleischer rings) allowed us to exclude the diagnosis of hemochromatosis and Wilson's disease." and (Page 9) "low levels of ferritin and no iron overload in the liver and/or spleen on MRI of the liver could exclude the diagnosis of hereditary hemochromatosis[1]. Wilson's Disease was also excluded because of normal range of ceruloplasmin and absence of ophthalmic signs (Kayser–Fleischer rings)[2]. Also alcoholic liver disease, non-alcoholic fatty liver disease and infective forms of hepatitis was excluded. However, a thorough genetic examination is needed to verify that the patient has no genetic disorders related to liver cirrhosis such as hereditary hemochromatosis, Wilson's disease and alpha-1 antitrypsin deficiency. During her hospital stay, the PLT count was sometimes less than $50 \times 10^9$/L and transfusion effect is poor, so liver biopsy was not considered. According to Roulot et al[3], the liver abnormalities in TS patients are mainly caused by congenital vascular disorders. Considering the unknown origin of cirrhosis, genetic disease detection or liver biopsy is needed when it is permitted. " We consider a thorough panel of genetic disorders for cirrhosis needed, owing to the epidemic control, this patient could not return to hospital in a short time, we will do it in the near future.

Thank you for your question again.

5. Was a liver biopsy considered? If not, please explain and discussed.

**Revision 5:** Thank you for your remind. Liver biopsy can help determine the cause of cirrhosis. We have discussed the necessity of liver biopsy and why we have not perform it in the discussion section "During her hospital stay, the PLT count was sometimes less than $50 \times 10^9$/L and transfusion effect is poor, so liver biopsy was not considered. According to Roulot et al[3], the liver abnormalities in TS patients are mainly caused by congenital vascular disorders. Considering the unknown origin of cirrhosis, genetic disease

detection or liver biopsy is needed when it is permitted. ” (Page 9).

6. it is well recognized that low platelet and/or red blood cell counts are observed as side effects of ruxolitinib, can the authors be more detailed regarding the timing of treatment and provide more detailed in the discussion about ruxolitinib.

**Revision 6:** Thank you for your advice. Though it is well recognized that low platelet and/or red blood cell counts are observed as side effects of ruxolitinib, Cervantes et al[4] and Verstovsek et al [5] believe that it's unnecessary to delay or withhold ruxolitinib because of co-existent or treatment related anemia. We have introduced the usage of ruxolitinib in detail: “Ruxolitinib was intermittently used based on the blood platelet count. The recommended starting dose is 5mg or 10 mg twice daily (b.i.d.), depending on platelet counts (≥ 50 to < 75 × $10^9$/L, 75 to 100 × $10^9$/L, respectively) regardless of Hb level. When the blood platelet count < 50× $10^9$/L, ruxolitinib use is recommended to cease. ” (Page 8). We also discussed the usage and effect of ruxolitinib in the discussion section: “Ruxolitinib is discontinued when the blood platelet count < 50× $10^9$/L. Most of patients with myeloproliferative neoplasms can achieve a ≥ 50% reduction in palpable spleen length at any time during the treatment with ruxolitinib[4]. The level of myelofibrosis was reduced after ruxolitinib treatment, however, significant splenomegaly was observed in this patient after 48 wk treatment with ruxolitinib, Hypersplenism may be the main cause of pancytopenia instead of the side effect of ruxolitinib. Therefore, we consider the blood routine does not represent his true level, we make treatment plan of ruxolitinib which is correlate with Devos et al[3].” (Page 9-10).

7. I did not find any discussion regarding the gene mutations found in this patient in relation with the presentation of symptoms and other related

pathologies. Even though the authors mentioned the article has been revised by an English native speaker, I did find many grammatical errors and typos thorough out the manuscript, thus the English needs to be significantly improved.

**Revision 7:** The reviewer has made a very good point here. The question raised by the reviewer would provide valuable information to our study. The patients is diagnosed as primary myelofibrosis(PMF) with mutation of *MPL* and *SH2B3*, though *MPL* and *SH2B3* is considered as poor prognostic factors in essential thrombocythemia (ET) patients, whether *MPL* and *SH2B3* have inferior outcome or have some negative correlation with pathologies is unknown. We have clearly clarified is the discussion section: "In essential thrombocythemia patients, mutation in *SH2B3* was found to be an additional negative prognostic factor[5], which has not been clearly demonstrated in PMF. Though it is recognized that *MPL* is associated with higher risk of fibrotic progression in essential thrombocythemia [6], definitive conclusions regarding the impact of *MPL* and *SH2B3* mutations on prognosis or other pathological changes are difficult due to the fact that less than 10% of patients with PMF harbor alternations in the *MPL* gene[7] and the rarity of *SH2B3* mutations in PMF patients." (Page 10).

As you suggested, we have sent the article to "Filipodia" for language polishing, hope it will reach the requirements of this journal.

Thank you very much! Happy new year!

Comments to the author:

Reviewer #2:

The case report discusses Turner syndrome presenting with primary myelofibrosis. The patient also has coexistent cirrhosis and large ovarian cyst.

1. Authors have documented the genetic mutation for PMF. The abdominal imaging clearly shows large ovarian cyst in the patient. Authors have done CT scan of abdomen. However, ultrasonography abdomen and MRI abdomen are essential to look for nature of ovarian cyst whether it is benign or malignant. The CT scan is useful for N and M staging of malignant ovarian lesion.

**Revision 1:** Thank you for your remind, maybe we do not make some clear statements or have not mention the abdominal ultrasound and magnetic resonance examination. We have added some details to the "*History of present illness*" section as: "Magnetic resonance and enhancement revealed cirrhosis, splenomegaly, and a large cystic mass in the right ovary. However, no further details regarding cirrhosis and the cystic mass obtained." (Page 5). We also add "Abdomen ultrasound shown a huge cystic mass measured as 30 mm × 148 mm on the right side of ovarian, which is considered as a serous cystadenoma."(Page 7) to the section of "*Laboratory examination*".

All ultrasonography abdomen and MRI abdomen in our hospital or other clinic considered large ovarian cyst as benign.

2. In the present case primary myelofibrosis can also cause non-cirrhotic portal hypertension by causing splenomegaly. Therefore, unless there is transient elastography or liver fibrosis markers or liver biopsy it may be early to say that patient also has cirrhosis of liver. Authors have reported a good clinical case which is worth reporting. However few issues should be cleared.

**Revision 2:** Thank you for your advice. We agree that our statements were too definitive, and we have edited the examination of liver fibrosis markers

(Table 3). The elevated liver fibrosis marker may illustrate the cirrhosis of liver, however, we have not preform liver biopsy, we have listed the limitations of our case, “However, a thorough genetic examination is needed to verify that the patient has no genetic disorders related to liver cirrhosis such as hereditary hemochromatosis, Wilson’s disease and alpha-1 antitrypsin deficiency. During her hospital stay, the PLT count was sometimes less than $50 \times 10^9$/L and transfusion effect is poor, so liver biopsy was not considered. According to Roulot et al[3], the liver abnormalities in TS patients are mainly caused by congenital vascular disorders. Considering the unknown origin of cirrhosis, genetic disease detection or liver biopsy is needed when it is permitted. “(Page 9).

Thank you for your kind again, Happy new year!

## References:


1. Wu, L., Zhang, W., Li, Y., Zhou, D., Zhang, B., Xu, A., Wu, Z., Wu, L., Li, S., Wang, X., Zhao, X., Wang, Q., Li, M., Wang, Y., You, H., Huang, J., Ou, X., Jia, J.,Wu, L., Zhang, W., Li, Y., Zhou, D., Zhang, B., Xu, A., Wu, Z., Wu, L., Li, S., Wang, X., Zhao, X., Wang, Q., Li, M., Wang, Y., You, H., Huang, J., Ou, X., Jia, J. Correlation of genotype and phenotype in 32 patients with hereditary hemochromatosis in China. *Orphanet J Rare Dis 2021; 16*1; 398 [PMID: 34583728 doi:10.1186/s13023-021-02020-y]
2. Kasztelan-Szczerbinska, B., Cichoz-Lach, H.,Kasztelan-Szczerbinska, B., Cichoz-Lach, H. Wilson's Disease: An Update on the Diagnostic Workup and Management. *J Clin Med 2021; 10*21 [PMID: 34768617 doi:10.3390/jcm10215097]
3. Roulot, D., Degott, C., Chazouillères, O., Oberti, F., Calès, P., Carbonell, N., Benferhat, S., Bresson-Hadni, S., Valla, D.,Roulot, D., Degott, C., Chazouillères, O., Oberti, F., Calès, P., Carbonell, N., Benferhat, S., Bresson-Hadni, S., Valla, D. Vascular involvement of the liver in Turner's syndrome. *Hepatology 2004; 39*1; 239-247 [PMID: 14752843 doi:10.1002/hep.20026]
4. Cervantes, F., Ross, D. M., Radinoff, A., Palandri, F., Myasnikov, A., Vannucchi, A. M., Zachee, P., Gisslinger, H., Komatsu, N., Foltz, L., Mannelli, F., Passamonti, F., Gilotti, G., Sadek, I., Tiwari, R., Zor, E., Al-Ali, H. K.,Cervantes, F., Ross, D. M., Radinoff, A., Palandri, F., Myasnikov, A., Vannucchi, A. M., Zachee, P., Gisslinger, H., Komatsu, N., Foltz, L., Mannelli, F., Passamonti, F., Gilotti, G., Sadek, I., Tiwari, R., Zor, E., Al-Ali, H. K. Efficacy and safety of a novel dosing strategy for ruxolitinib in the treatment of patients with myelofibrosis and anemia: the REALISE phase 2 study. *Leukemia 2021; 35*12; 3455-3465 [PMID: 34017073 doi:10.1038/s41375-021-01261-x]
5. Zhou, A., Afzal , A., Oh, S. T.,Zhou, A., Afzal , A., Oh, S. T. Prognostication in Philadelphia Chromosome Negative Myeloproliferative Neoplasms: a Review of the Recent Literature. *Curr Hematol Malig Rep 2017; 12*5; 397-405 [PMID: 28948488 doi:10.1007/s11899-017-0401-2]
6. Ross, D. M., Babon, J. J., Tvorogov, D., Thomas, D.,Ross, D. M., Babon, J. J., Tvorogov, D., Thomas, D. Persistence of myelofibrosis treated with ruxolitinib: biology and clinical implications. *Haematologica 2021; 106*5; 1244-1253 [PMID: 33472356 doi:10.3324/haematol.2020.262691]
7. Piasecki, A., Leiva, O., Ravid, K.,Piasecki, A., Leiva, O., Ravid, K. Lysyl oxidase inhibition in primary myelofibrosis: A renewed strategy. *Arch Stem Cell Ther 2020; 1*1; 23-27 [PMID: 33738462 doi:10.46439/stemcell.1.005]