Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: The authors describe an interesting case of ATTRwt amyloidosis with severe heart failure in a relatively young male patient. This is important since ATTR amyloidosis is still overlooked and underdiagnosed all over the world, and since the disease also can affect younger patients. The manuscript is generally well written and the diagnostic work-up seems appropriate and is quite well described. However, some revisions are needed before the manuscript is ready for publication.

1.Title: Although 58 years of age is relatively young for a patient with severe ATTRwt cardiomyopathy, I wouldn't consider him a young patient. Therefore, please consider revising the title somewhat.
Thank you for the suggestion. The title is modified to "An Early and Aggressive presentation of Wild-type Transthyretin Amyloid Cardiomyopathy"

2. Abstract: Please see above.
We have made changes to the abstract. Our abstract line now reads as "We report an unusual case of a 58-year-old patient with ATTRwt cardiomyopathy requiring heart transplantation"

3. Introduction: The introduction is very short and is lacking references. Please update and add some key references to give the reader some more background information.
We have updated the introduction and added background information on ATTR-CM with citations.
"ATTR-CM is an infiltrative, progressive, and potentially fatal cardiomyopathy that is caused by extracellular deposition of misfolded transthyretin-derived insoluble amyloid fibrils in the myocardium."

4. History of past illness: Please add information about any history of arrhythmias, which is also common in these patients.
We have modified history of past illness. We have added the following sentence to manuscript: Other than atrial fibrillation, he had no significant history of other arrhythmias.

5. Personal and family history: There is no information on the race of the patient. This would be of interest since ATTRwt amyloidosis seems to be more common in Caucasian males, whereas ATTRv amyloidosis (ATTRV122I) is more common in Afro-Americans. Please add this information if available and if permitted.

Our history of present illness now includes race of the patient. We have modified the line as follows: "A 58-year-old, Caucasian man presented to the heart failure clinic.."

6. Further diagnostic work-up: Please add information on cardiac rhythm also here.
We have added the following line to our manuscript under further diagnostic work up section: "ECG showed AV-paced complexes and low voltage in both limb and precordial leads."

7.Was the Tc PYP scan graded according to the Perugini scale? If not, please state what grading that was used.
Thank you for pointing out. The scan was graded according to Perugini scale. Our sentence in manuscript was modified as "A technetium pyrophosphate scan (Tc PYP) showed a heart/contralateral lung ratio of 1.77 and visual grade 3 as per the Perugini scale"

8.Finally, regarding the genetic testing, which genes were screened and what were the two "genes of unknown significance"? An unremarkable screening of the TTR gene should be the bottom line here.
We have added the specific variants and clarified in the final diagnosis section as well. Thank you for your comments. The sentence in manuscript was modified as below: "Genetic testing was performed and was unremarkable, showing two variants of unknown significance, c.3262-3C>G in the LAMA4 gene and p.K963E in the RBM20 gene. Screening of the TTR gene was unremarkable ruling out hereditary TTR cardiomyopathy."

9. Final diagnosis: I agree that ATTRwt amyloidosis was the most likely etiology since ATTR was found in the endomyocardial biopsy if both AL and ATTRv amyloidosis has been ruled out. However, a negative genetic testing needs to be clearly stated in the previous section in order for this to apply.
Agree. Thank you for suggestion. The genetic testing results are now clearly stated as mentioned above.

10. Discussion: Although it's not known yet it would be nice if the authors could speculate a bit about why some patients are affected earlier from ATTRwt amyloidosis. In our experience, long-distance athletes and heavy workers seem to be at risk for early disease development.
Thank you for sharing your experience. Our patient was a heavy worker too. He was a construction worker. On literature review, we could not find a particular reason to why some people develop ATTRwt early on at age less <60 years. We agree that this should be looked in future studies that what patient characteristics predispose to early onset of ATTRwt cardiomyopathy.

Following lines were added to the manuscript: "After review of the literature, it remains uncertain why some individuals may be predisposed to developing ATTRwt at an earlier age."

11.Also, the non-biopsy diagnosis of ATTR cardiomyopathy (first described by Gillmore et al) is now widely accepted and deserves to be mentioned.
Thank you for the suggestion. Following line is added to manuscript along with the citation: "The non-biopsy diagnosis of ATTR-CM with TcPYP scan (first described by Gillmore et al) is now widely accepted and has replaced the historical endocardial biopsy provided AL amyloidosis is ruled out."

12.Finally, tafamidis is the only drug approved for ATTR cardiomyopathy so far, although trials with patisiran, vutrisiran, inotersen and eplontersen are underway. Please update accordingly.
The following line is added to manuscript to reflect this change: "Tafamidis is the only drug approved for ATTR cardiomyopathy so far, although trials with patisiran, vutrisiran, inotersen and eplontersen are underway."

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Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: We believe that this is a rare case of ATTR amyloidosis diagnosed at a young age with severe HFrEF that deserves to be reported.

#1 Was there anything in the extracardiac findings such as carpal tunnel syndrome?
There were no extracardiac findings. This was added to our manuscript. Thank you for your comments. The following line was added to the HPI: "On review of symptoms, the patient had no palpitations, carpal tunnel symptoms, neuropathy, or back pain."

#2 The authors should add about physical examination, such as physique, vital signs, etc.
Thank you for suggestion. Following line was added in manuscript to include this change: "Vital signs depicted borderline systolic blood pressure of 95/70 mmHg with mean of 78 mmHg, normal heart rate, normal respiratory rate and saturation on room air, and normal temperature."

#3 The authors should comment on ECG findings.
The following line was added in manuscript to include ECG findings: "ECG showed AV-paced complexes and low voltage in both limb and precordial leads."

#4 The authors should add the following information about echocardiographic findings and figures; Left ventricular inflow waveform (E/A, DcT, etc.), GLS (presence of apical sparing).

Thank you for suggestion. We have added this information in the manuscript along with images. Unfortunately, the GLS was not performed at time of acquisition of echocardiogram and hence, we could not include strain images. Following lines were added to the manuscript:

"Diastology additionally showed an E/A ratio of 3.3, severely reduced mitral annular tissue velocities (e' medial of 3 cm/s and e' lateral of 5 cm/s), E/e' of 25, and deceleration time (DT) time of 141 ms (Figure 1d)."

Also, since the readers do not know if there is left ventricular wall motion reduction, it would be easier to understand if the authors could show the diastole and systole figures side by side.

The figure showing 4-chamber view of LV in systole and diastole side-by-side is added to manuscript.

Also, is there a mild pericardial effusion?

Yes, thank you for mentioning. We have included in the manuscript that there was a trivial pericardial effusion.

#5 The authors showed a macroscopic figure of the cardiac transplant, but the readers are not sure of the size of heart, thus, the authors should have a picture with the scale included. After all, the authors should show figures of the histology, especially the immunostaining of ATTR.

Thank you for the suggestion. We have removed the gross heart image as we do not have a scale. We have included histology images of native heart tissue with congo red staining in the manuscript (Figure 4).

#6 This case has undergone cardiac transplantation, but it is not a fundamental treatment for amyloidosis, and the possibility of amyloid deposition again cannot be ruled out. The authors should discuss whether there are any such reports, and whether or not there is any preventive effect of oral medication to prevent the deposition of amyloid again.

This is a very good and thoughtful point. Even though cardiac transplantation is not a fundamental treatment of amyloidosis, the current consensus scientific statement from the American Heart Association recommends cardiac transplantation can be used in patients with Stage D heart failure, like our patient.(1)

After careful review of literature, we were unable to find studies suggesting which medications or strategies to use to prevent post-transplant deposition of amyloid fibrils in the graft. We agree with you that this is the area of further research as number of heart transplant patients secondary to ATTRwt

cardiomyopathy continue to rise. We continued our patient on Tafamidis post transplant.

We added following lines to the manuscript: "As there are very few cases of heart transplantation for ATTR-CM reported in the literature given that most patients have a median age of 80, it remains to be studied how best to prevent the deposition of amyloid again in the transplanted heart. Our patient remains on Tafamidis post-transplant with the hope of stabilizing TTR protein tetramer and preventing amyloid fibrils from depositing in the myocardium."

Reference:

(1) Kittleson MM, Maurer MS, Ambardekar AV et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation 2020;142:e7-e22.