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Reviewer A

Comment 1: Authors can potentially increase the value of the paper by providing some more images (ecocardiography, pre-and post-treatment evaluations...)

Reply 1: Thank you for your comments and your dedication. We provided some images about treatment response of both patients (see Figures 2 and 4). Unfortunately, we are not able to provide echocardiography images.

Comment 2: Please report genes in italics and proteins non in italics

Reply 2: We put genes in italics and proteins in non-italics as proposed (see lines xxx).

Changes in the text: Changed from "ROS1" to "*ROS1*" and from "ALK" to "*ALK*".

Reviewer B

Comment 3: The background had been dealt with too briefly. For example the NBTE frequency are missing.

Reply 3: we added some data about NBTE frequency (see page 2, line 44)

Changes in the text: "It is very infrequent though, being estimated an overall incidence between 0.9% and 1.6% in autopsy populations."

Comment 4: References about NBTE and ALK/ROS1 rearrangements are missing.

Reply 4: We did not find recent and quality references relating directly NBTE and ALK/ROS1 rearrangements.

Changes in the text: We could not add new information so there is no change in that case.

Comment 5: Malignancy is the most frequent cause of NBTE: this part deserves development with lung cancer the leading malignant cause of TE but also NBTE? What are the other causes?

Reply 5: We added some data on this topic in order to be more specific (see page 2 lines 45 to 47).

Changes in the text: “Malignancy is the most frequent cause of NBTE, causing up to 75% of cases, and being lung cancer the most prevailing malignant cause (28% of malignant-related NBTE), while the remaining 25% correspond to non-malignant causes, like systemic lupus erythematosus.”

Comment 6: Choose between NBTE or marantic endocarditis

Reply 6: We prefer NBTE as is a more precise form to refer to the disease.

Changes in the text: See page 2 line 45, we changed the concept “marantic endocarditis” for “NBTE”.

Comment 7: Add EGFR mutation on what is known section

Reply 7: As proposed, information about *EGFR* mutation has been added (see in page 1, line 29).

Changes in the text: “EGFR mutation is also related to such thrombotic complication, although less frequently”.

Case 1:

Comment 8: If the second line treatment was planned on September 2022. Could we know others key dates as NBTE diagnosis, lorlatinib initiation, cardioembolic accident date, time to normalize blood test? objective response confirmation date?

Reply 8: We have added precise information about timeline of key events (see page 2 lines 72 and 81, page 3 lines 87-88 and 91-92) in order to make comprehensible the chronology of the clinical case.

Changes in the text: Dates were added on the mentioned lines. “Days before the appointment to initiate treatment, the 09/09/2022...”. “...a transthoracic echocardiography (TTE) was performed the 09/12/2023...”, “Lorlatinib was initiated in crushed form in a dilution through a nasogastric tube the 09/14/2023”, “...partial neurological improvement were achieved by 09/19/2023”, “Objective response to lorlatinib was confirmed in the brain the 12/13/2022...”.

Comment 9: How the infective endocarditis was ruling out?

Reply 9: We ruled out infective endocarditis through blood cultures that resulted negative, as well as the absence of other clinical data as fever or chills (see page 2, lines 81-83 and page 3, line 115).

Changes in the text: We did not make any changes in this case. The sentences are: “After ruling out infective endocarditis with negative blood cultures, she was finally diagnosed of NBTE with associated DIC”, “To rule out a cardioembolic mechanism, a TTE was performed, showing no

significant results. However, the transesophageal echocardiography (TEE) revealed an aortic valve vegetation. Along with negative blood cultures, the diagnosis of NBTE was confirmed.”

Comment 10: Update the follow-up. When were the last news?

Reply 10: We added new information about the latest patient’s status, being alive and showing good Performance Status in October 2023, a year after initiating lorlatinib (see page 3 lines 91-93). She had an intracranial progression being treated with focal Radiotherapy and kept on lorlatinib.

Changes in the text: Lines 91-94 we added “She presented in September 2023 brain progression treated with focal radiotherapy (total dose 20 Gy) and continued on lorlatinib treatment. In October 2023 patient was currently able to talk, walk with a stick and eat normally, with correct tolerability to treatment.” After “... brain MRI”.

Case 2:

Comment 11: Add a temporality between lung ADK diagnosis and second presentation to emergency service please (both in November 2022, which was the first?)

Reply 11: We added temporality in the text to make clear the sequence of events (see page 3, lines 101 and 105-106).

Changes in the text: Line 101 we added “Three weeks later, on 10/14/2022 he consults the emergency service for cervical palpable mass.” Line 105 we added “the 11/11/2022, two days after the cancer diagnosis was made” and “emergency department” after “the first consultation”.

Comment 12: Specify the grade for anemia and PAL increase.

Reply 12: We added the specified grades of anemia and PAL increase (see page 3 line 108) as per CTCAE v5.0.

Changes in the text: In line 109 we added “grade 2” after “alkaline phosphatase” and “grade 1” after “mild anemia”.

Comment 13: Update the patient follow-up. Since January 2023, what happens?

Reply 13: We updated the patient’s follow-up as requested, showing his status and his treatment response (see page 3, lines 120-122).

Changes in the text: In line 120 we added “Due to persistent grade 2 neutropenia the patient needed dose reduction of crizotinib to 200mg/12h, but on October 2023 the patient kept on good performance status and no signs of progression”, at the end of the paragraph.

Discussion

Comment 14: L126: “TE can be associated with...” add in lung cancer patients

Reply 14: We changed the text as advised (see line 127 in page 3).

Changes in the text: “TE can be associated with poor prognosis and shortened PFS in lung cancer patients”.

Comment 15: L126-129. The meaning of this sentence is unclear. Of course patients with lung cancer presents higher mortality than other patients with benign underlying conditions, NBTE or not.

Reply 15: We modified the sentence in order to be more accurate and clearer (see page 3, lines 127-129).

Changes in the text: We changed the sentence to “Specifically, when analysing patients diagnosed of NBTE, the subpopulation presenting lung cancer show higher mortality in 1 year than patients with other malignant underlying conditions”.

Comment 16: 75% of NBTE case are cancer-associated, so the remainder are non-cancer etiology. Precision is necessary. (Rahouma M, Khairallah S, Dabsha A, Elkhartbotly IAMH, Baudo M, Ismail A, Korani OM, Hossny M, Dimagli A, Girardi LN, Mick SL, Gaudino M. Lung Cancer as a Leading Cause among Paraneoplastic Non-Bacterial Thrombotic Endocarditis: A Meta-Analysis of Individual Patients' Data. *Cancers (Basel)*. 2023 Mar 20;15(6):1848.)

Reply 16: Thank you very much for your comment and your precision, as given by the reference. We added the clear data of the mentioned reference to add more precision to our manuscript, and we put the information on the background where initially we speak about this phenomenon’s frequency (see page 2, lines 45-47).

Changes in the text: We changed the text in lines 45 to “Malignancy is the most frequent cause of marantic endocarditis, causing up to 75% of cases, and being lung cancer the most prevailing malignant cause (28% of malignant-related NBTE), while the resting 25% correspond to non-malignant causes, like systemic lupus erythematosus.”

Comment 17: Speak about “sterile thrombotic friable cardiac vegetation” instead of “mass”

Reply 17: We changed the text as advised (see page 3, line 130).

Changes in the text: “NBTE is a thrombotic paraneoplastic phenomenon characterised by cardiac sterile thrombotic friable cardiac vegetation composed of fibrin and platelet aggregates.”

Comment 18: L146. Precision about modified Duke criteria is necessary

Reply 18: We added information from the latest revisions of Duke criteria on infective endocarditis (see page 4, lines 144-148).

Changes in the text: The final text form is “It is necessary to rule out infective endocarditis by the modified Duke criteria. Infectious endocarditis should be considered when presenting two major diagnostic criteria like microorganism identification on 2 or more separate blood cultures, vegetation seen on cardiac valve through echocardiogram or abnormal metabolic

activity on cardiac valve on PET-CT, or presenting multiple minor criteria like documented fever, documented cerebral or splenic abscess, immunologic phenomena like Osler nodes or positive rheumatoid factor.“

Comment 19: L148-150 “Unfractionated heparin...associated with neoplasm. Add reference

Reply 19: We changed the information as it was not precise enough (see page 4, lines 150-152) for new contrasted information to make the manuscript more valuable. We changed the reference for the correct one, which is the American Hematology Society guidelines in thrombosis prevention and treatment in cancer patients from 2021, already cited in the text.

Changes in the text: The sentence final form is “Unfractionated heparin, LMWH and warfarin can decrease the risk of embolization and thrombotic recurrence, though some studies suggest more efficacy from heparin than vitamin k inhibitors reducing the risk of recurrent thrombosis”. We added the corresponding number of the reference after the new sentence.

Comment 20: L150-152. An “acceptable alternative “ can not be based on a clinical case report (only reference provided)

Reply 20: The reference has been changed for the American Hematology Society guidelines from 2021 that support the use of heparin and direct oral anticoagulants (DOACs) (see page 4, lines 152-155).

Changes in the text: We added “apixaban” to the list of DOACs and we added “are equally acceptable alternatives but should be used carefully in patients with gastrointestinal or genitourinary tracts tumors”.

Comment 21: L153-155. It would be interesting to develop this section with the lung cancer background

Reply 21: We developed it on the background, too (see page 2, lines 47-50). We found no new information on surgical approach in lung cancer patients presenting NBTE.

Changes in the text: The next text was added in the background: “Medical treatment includes anticancer treatment, anticoagulation with heparin, direct oral anticoagulation (DOAC) or vitamin k antagonists [4]. In some cases, surgical approach may be necessary, in a case-by-case basis (if presence of heart failure, big valve vegetations or medical treatment failure with recurrent embolism).”

Comment 22: L157 Change EET for TEE and ETT for TTE (as in case description)

Reply 22: We modified the text as advised (see line 159 page 4).

Changes in the text: “TEE” and “TTE” in line 159.

Comment 23: Develop less about the patient treatment and more about Lazarus effect

Reply 23: As advised, we talked more about the Lazarus effect presented by the patient in the case 1 section (see page 3, lines 88-91) and in the discussion section (see page 4, lines 162-164).

Changes in the text: Lines 88-91 we added: "with resolution of tetraplegia (with a gain in motor function of the four limbs, being able to walk with help), improving the level of consciousness to Glasgow 15 and with partial resolution of aphasia." Line 164: "being able to walk with a stick and to have simple conversations, with just residual bradyphasia". The last sentence of the paragraph (lines 164-166) has been changed to "This case emphasizes the need to establish early antitumoral treatment due to potential Lazarus effect [10] expected from these highly active drugs, as seen in that patient."

Comment 24: L175-176: Add a sentence about lung cancer-induced NBTE prognosis please.

Reply 24: We described some relevant prognosis information seen in reports about lung cancer-induced NBTE (see page 4, lines 176-178), properly referenced.

Changes in the text: We added the next information in lines 176-178 "as seen in some reports 79% of patients can have an embolic event 1 month after the NBTE diagnosis and being the 3-month estimated overall survival of 26% of patients diagnosed of lung cancer induced NBTE."

Conclusion:

Comment 25: L181 not to change but to improve prognosis

Reply 25: We changed the text as advised in order to be more accurate (see page 4 line 185).

Changes in the text: We modified the word "change" for the concept "improve".

Reviewer C

Comment 26: Line 65: Please describe pregnancy and birth history. Antiphospholipid syndrome (APS) must be ruled out.

Reply 26: We added information on the birth history of the patient (see page 2 lines 61-62) but antiphospholipid syndrome was not ruled out at that moment.

Changes in the text: We added "two healthy children and no history of abortions" after "past medical history" at line 61.

Comment 27: Line 70: What is the reason you did not switch from heparin to a DOAC (ex. apixaban) with less risk of bleeding?

Reply 27: We kept heparin for the first months as per recommendation of the Vascular Medicine team that assessed the patient when the first thrombotic event was diagnosed. In case of bleeding event it could be controlled with its antidote.

Changes in the text: We added the information “that was maintained per recommendation of Vascular medicine department” after low molecular weight heparin (see line 66 in page 1).

Comment 28: Lines 70-71: How often have you evaluated brain metastases? What are the modalities?

Reply 28: The initial evaluation on brain metastases was made by monthly brain MRI the first 3 months and thereafter by brain MRI every 3 months.

Changes in the text: We added “assessed by brain MRI” after “7 months” (see page 2, line 67).

Comment 29: Line 91: Did you administer lorlatinib in crushed form? Please describe the dosage form.

Reply 29: Lorlatinib was administered in crushed form and in a dilution through nasogastric tube (see line 87).

Changes in the text: We explicit de information on line 87 by adding “in crushed form in a dilution”.

Comment 30: Lines 98-100: Have you evaluated this patient's heart for coronary artery stenosis or atrial fibrillation?

Reply 30: In this patient, atrial fibrillation was ruled out by EKG, but no coronary artery stenosis was ruled out, although the echocardiogram showed no signs of cardiac ischemia.

Changes in the text: We added new information on EKG results: “Atrial fibrillation was ruled out by electrocardiogram.” (see lines 99-100).

Comment 31: Line 125: I consider reference 3 to be inappropriate as a citation.

Reply 31: We appreciate your comment and, in order to improve the manuscript quality, we skipped the mentioned citation.

Changes in the text: The reference “Landi L, Chiari R, Tiseo M, et al. Crizotinib in MET-Deregulated or ROS1-Rearranged Pretreated Non-Small Cell Lung Cancer (METROS): A Phase II, Prospective, Multicenter, Two-Arms Trial. Clin Cancer Res. 2019;25(24):7312-7319.” has been erased from the manuscript.

Comment 32: Line 157: Can you explain the abbreviation for EET and ETT?

Reply 32: It has been a transcription mistake, as it was supposed to be “TEE” and “TTE”, corresponding to transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). It has been corrected by the correct form on lines 113-114.

Changes in the text: Lines 113 and 114 we changed “EET” for “TEE” and “ETT” for “TTE”.

Comment 33: Have you evaluated for DVT or PE in case 2?

Reply 33: Case 2 was evaluated for PE through thoracic CT scan, which ruled out that diagnosis, but there was no echography evaluation for DVT on limbs.

Changes in the text: Lines 115-116 has been added the next information “No echography was made to rule out deep vein thrombosis of limbs, but CT scan ruled out pulmonary emboli.”

Comment 34: Please describe the MRI imaging conditions in the legend for Figure 1 and Figure 2. Also, please add a Diffusion-weighted image.

Reply 34: As advised, we described the MRI imaging in the legend of Figure 1 and we added a diffusion-weighted image of the brain conditions on multiple ischemic affection.

Changes in the text: we added to the figure 1 legend: “Left: multiple subacute ischemic affection of the brain in a frontoparietal, occipital and cerebellar disposition, due to cardioembolic mechanism. Right: Diffusion-weighted image from the same patient, showing ischemic lesions.”

Comment 35: Please add a note on whether the risk of incidence of NBTE is higher in cases with DVT than in cases without DVT.

Reply 35: we did not find high-quality evidence of existing a higher risk of NBTE in cases of DVT compared with no DVT.

Changes in the text: As we found no clear evidence, we did not modify the text in this case.