Peer Review File

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Review comments

Reviewer A

The authors present a case report of a patient with a large thymoma and trisomy 21.

1. I do not think that this report substantially contributes to our knowledge about the diagnostics or therapy of thymomas. The association with trisomy 21 may be a mere coincidence.

   REPLY: We are sorry that the reviewer did not appreciate this report. We believe that the novelty is mainly the combination of two pathologies that have never been described together. Moreover, Down Syndrome is associated with a low incidence of solid tumor and often patients with this syndrome show a premature regression of the thymic gland. However, we extensively modified the text. We hope that reviewer could like this effort.

2. The fact that "Due to the presence of AbACh-Receptor antibodies, stage I Myasthenia, according to the Myasthenia Gravis Foundation of America (MGFA) classification, was diagnosed… "contradicts the title of the manuscript according to which the patient was asymptomatic.

   REPLY: We agree with the author with this affirmation, so we modified the text in order to better clarify this issue. Ocular symptoms were found to be poorly assessable in consideration of the typical facies of the patient with Down syndrome. Furthermore, due to the patient's mental retardation, the anamnesis was difficult to collect. Our neurologists, however, evaluated the patient's condition and the positivity of the antibodies, they preferred to classify him as reported in the text.

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3. Concerning the title (and the abstract as well), it would be advisable to specify the

thymoma type here and not only later in the text.

REPLY: Thank you for your kind advice, we have modified the title and part of the abstract.
Changes in the text: Title.

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4 I am also wondering that all 8 authors of the paper are surgeons whereas all 4 figures are radiologic images. Thus, if this paper should be published in another journal, it might be accurate to involve experts also of other disciplines such as radiology. Not speaking about the fact that a pathologist has not been involved and that the paper lacks any histology.

REPLY: Thank you for the advice, we have involved our dedicated pathologist (the same who analyzed both the core biopsy and the specimen) for the revision of the manuscript and add her as coauthor. Moreover, we added a figure of the main histological features.
Changes in the text: We added pathologist to the authors list

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Reviewer B

The authors report interesting case "An asymptomatic giant thymoma in a patient with trisomy 21: a case report". Even though there are many case reports published on this theme, I think this work merits attention and I have some suggestions for further improvement:

1. The title should be modified, as there was diagnosed myasthenia gravis (According to MGFA clinical classification Class I patients may have any ocular muscle weakness among others): There should be specified the cardiorespiratory symptoms rather than only the term asymptomatic.

REPLY: In this case, ocular symptoms were poorly assessable, and in accord with our neurologists, evaluated the patient's condition and the positivity of the antibodies, they preferred to classify him as a class 1.
Nevertheless, the patient did not present apparently any neurological, oculars nor cardiorespiratory, therefore we preferred to synthesize with "asymptomatic". Nevertheless, the text has been modified to better clarify this issue.

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2. Similarly, throughout the text cardiorespiratory symptoms should be mentioned when described the symptoms for instance line 79 ``completely asymptomatic`` may be wrong.

REPLY: The text has been modified

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3. Patients with Down Sy. are mentally retarded patients and this may be a limitation when describing symptoms. This fact should be somehow incorporated in the text. I suggest also to provide information for eventually previous hospitalizations.
   REPLY: Thanks for the clarification, the text has been modified.

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4. The discussion should be thoroughly revised. There are many repetitions from the introduction section (lines 109-116). Furthermore, in my opinion there are many superfluous well known general information (lines 134-141). Instead, there may be discussed and compared your study with other studies reporting giant thymomas in relation to the type of thymoma, symptoms, resectability, outcome…… These can be included in any small table, such as Table 1.
   REPLY: The discussion has been extensively reviewed also in the light of your consideration.

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5. I think the actual Table 1 is superfluous and should be omitted.

REPLY: Thank you for your suggestion but we believe that reporting, so scheduled in a table, all those humoral markers allow us to make the text clearer and more readable.

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6. Minor issue: The term preoperatory or postoperatory in the figure legends may be used uniformly and corrected to preoperative or post-operative as you emphasized in the line 146 in the text.

REPLY: Text has been modified.

Reviewer C

Thank you very much for the opportunity to review the paper titled "An asymptomatic giant thymoma in a patient with trisomy 21: a case report". I have several major and minor comments.

Major comments

1. How was the patient staged for each (potentially) malignant lesion ? Was PET performed? Brain MRI?

REPLY: Thank you for your question, the preoperatory evaluation was not the same that is routinely performed due to the patient's condition. PET and brain MRI were not performed due to the real difficulty to remain still for the above-mentioned procedures.

Changes in the text: The text has been modified to clarify this issue

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2. Any anesthetic consideration performed given the large mass compressing the heart?

REPLY: Thank you for your consideration, the patient was evaluated with preoperative echocardiogram, without any signs of tamponade or congenital defect. Moreover, the patient had a pre-operative evaluation by our dedicated anesthesiologists.

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3. Please discuss any potential indication for adjuvant radiotherapy for stage III thymoma.

REPLY: Thank you for your consideration. Our policy is addressing all stage III thymoma to PORT. However, in this specific case, the patient had a real difficulty to stay still; hence, within the multidisciplinary board it has been decided to avoid PORT, also in consideration of the surgery radicality

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4. How long do the authors plan to follow up this patient?

REPLY: Patients with Thymoma and Myasthenia gravis are usually addressed to a dedicated surveillance plan that last at least 10 years after surgery. We added a reference to explain our policy

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Minor comments

5. More information on surgical techniques is required.

REPLY: The surgical description has been modified according to the reviewer comment.

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6. Typos and English syntax should be reviewed by an English expert and native speaker who is familiar with medical research.

REPLY: Thanks for the clarification, we provided an extensive review of the article.

Again, I appreciate the authors and the editor for providing me with this opportunity.

Reviewer D

Thank you for the peer review opportunity and thank you for reporting this very hard case.

I have some comments as follows:

- In the Abstract section, the authors addressed as follows "Up to 60% of the cases are asymptomatic (lines 38-39)", however; "Sixty percent of patients are symptomatic (line 56)" in the Introduction section. There is a discrepancy in the description. Please correct.

REPLY: The text has been modified.
Changes in the text: line 39

- The authors administrated the steroid as a perioperative therapy. Please clearly state the purpose of this treatment: is it management of MG? Tumor shrinkage? Also, what protocol was used to administer the steroid in the perioperative period? - Prednisone (line 88) should be listed as prednisone.

REPLY: Thank you for the consideration, prednisone was administered routinely in patient with thymoma and/or myasthenia gravis to prevent any MG exacerbation and to induce a tumor shrinkage. There is not a standard protocol since steroid therapy usually depends on the MG severity and is adjusted by the dedicated neurologist. The following reference may explain more in detail this issue:
Lucchi M, Van Schil P, Schmid R, Rea F, Melfi F, Athanassiadi K, Zielinski M, Treasure T; EACTS Thymic Working Group. Thymectomy for thymoma and myasthenia gravis. A survey of current surgical practice in thymic disease amongst EACTS members. Interact Cardiovasc Thorac Surg. 2012 Jun;14(6):765-70. doi: 10.1093/icvts/ivs046. Epub 2012 Feb 27. PMID: 22374292; PMCID: PMC3352719.
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Changes in the text:

- This case may have been difficult to intubation. Please include this point and describe what you noted regarding intraoperative anesthesia management.

REPLY: Thank you for your advice; fortunately, no anesthesiologic or intubation problems occurred during the surgery. The patient was thoroughly evaluated by our dedicated anesthesiologist pre- and intraoperatively. This aspect has been added to the text.
Changes in the text: None.

- Was the segmentally resected left phrenic nerve reconstructed?

REPLY: Thank you for your observation. In this case we did not proceed to a reconstruction of the phrenic nerve because the chest X-Ray showed a preoperative phrenic palsy. We usually tempt a nerve sparing surgery exclusively when the diaphragm is not pre-operatively impaired. Our policy regarding the nerve sparing surgery is reported in a previous paper (Aprile V, Bertoglio P, Korasidis S, Bacchin D, Fanucchi O, Dini P, Ambrogi MC, Lucchi M. Nerve-Sparing Surgery in Advanced Stage Thymomas. Ann Thorac Surg. 2019 Mar;107(3):878-884. doi: 10.1016/j.athoracsur.2018.08.071. Epub 2018 Oct 16. PMID: 30336118.)

- The re-operation was performed due to postoperative bleeding, where did the bleeding come from?

REPLY: Thank you for your question. This detail has been added.

- I consider that this case was asymptomatic because it was a thymoma type AB, a type of tumor that grows very slowly. I do not think this is that unusual.

REPLY: Thank you for your consideration. Despite the histology the mass was huge. This aspect has really impressed us, and this may explain why we have stressed this aspect in the manuscript.

Reviewer E

Congratulations to you on this rare case report. However, I still Have some questions in the following.

First, did any oncologist involved in the multidisciplinary tumor teamwork? Any plans of neoadjuvant therapy are considered in the case or the reason why not performing should be described.

REPLY: Thank you for your consideration. The priority was given to remove the mass before the eventual presentation of cardiorespiratory symptoms. The resection was pre-operatively judged as safe and feasible, and the MDB (that included a dedicate oncologist) decided to avoid any neoadjuvant treatment also due the patient conditions.

Changes in the text: None.

Second, I would recommend you place some intraoperative pictures or tumor specimen to better demonstrate the operative steps.

REPLY: Thank you for your valuable suggestion, unfortunately we don't have any intraoperative pictures, but we added some histological pictures as requested by other reviewers.

Reviewer F

The authors present a case report of the simultaneous occurrence of a thymoma and trisomy 21 in the same patient. The tumor had massive proportions (i.e., was "giant"),

but the fact that thymomas can grow to massive proportions and become giant is a well-known fact in the literature. The only original finding in this case report is the association with trisomy 21. Before the simultaneous occurrence of these two conditions can be ascribed any significance the authors need to establish a relationship between the two or explain how one influenced the other. This, unfortunately, has not been accomplished in this manuscript. The discussion and the description of the case report simply states that both conditions were present but there is no explanation as to the relevance of this finding and why we need to be aware of it. The data cited in the manuscript regarding the incidence of these tumors and the fact that biopsy is necessary to make a definitive diagnosis is also widely known and hardly a discovery of the authors.

REPLY: The text has been extensively modified according to the valuable comment of the reviewer. We stressed all the aspects that we judged as remarkable, with the hope that this effort made the text more interesting.

More specific issues:

The English needs to be carefully revised. There is improper English language throughout the manuscript that makes for confusing reading. One example is the use of the word "district" to indicate an anatomical compartment (line 53). This sentence should read "Large masses in this anatomic compartment….", etc. There are many others; it is recommended that the manuscript be reviewed by a native English-speaking person.

REPLY: The text has been extensively modified

The illustrations concentrate on the imaging of the lesion but there is no picture of the histology. At the very least an H&E of the biopsy demonstrating the relevant features should be provided.

The paper would benefit from having a pathologist as a co-author to assume responsibility for the diagnosis, particularly for a manuscript that purports to hinge its relevance in the pathology of the lesion. Thymoma diagnosis is quite controversial and difficult and requires the use of special stains to rule out lymphoid and other malignancies, especially for the WHO types B1 and B2. There is hardly a line in the manuscript regarding the histology to support the diagnosis rendered in this case.

REPLY: Our dedicated pathologist has been involved in the drafting of the manuscript. As rightfully suggested, we added a picture of the histological features of

the thymoma.

Changes in the text:

Reviewer G

The authors present an interesting case report of an asymptomatic giant thymoma in a patient with trisomy 21.

Major comments:

The initial core needle biopsy was diagnosed as type B2 thymoma, while the final diagnosis for the resection was type AB thymoma. Was the original biopsy misinterpreted as the wrong type of thymoma due to the presence of increased lymphocytes?

REPLY: Thank you for your question. The original biopsy was a core needle one with a few cells, the analyzed material was highly suggestive for a B2 thymoma. The whole specimen analyzed, however was labeled s AB thymoma. Surprisingly, with the benefit of hindsight, two others dedicate pathologists confirmed both the diagnosis. We do not believe in a misinterpretation, but the amount of the tissue is essential for a proper diagnosis.

Though the authors acknowledge this can change from biopsy to resection it should be clarified in the text, although it does not make a huge difference to the final management, it is a known diagnostic pitfall as lymphocyte rich AB thymomas exist and are often missed on resection, but more commonly on core needle biopsy - a topic that has recently been well covered; might want to include this reference [35034040]

REPLY: Thank you for your question. The text has been modified in the light of your valuable suggestion.

The conclusion states that "no sign of paraneoplastic syndrome associated" - does this mean you are ascribing myasthenia gravis to the thymoma rather than to trisomy 21? This should be clarified.

REPLY: Thank you for your question. The text has been modified to better clarify this aspect.

This manuscript needs to undergo extensive english language revision; altough there are little to no spelling errors it is extremely difficult to read the report as nearly every

sentence contains changes in tenses and grammatical errors with innaproriate use of adjectives, verbs, prepositions etc. This needs to be revised before this can be considered for publication in an English language journal.

Some examples/minor comments:

Abstract line 39-40: sentence needs to be edited; should read something like "several types of neoplasms can grow in this area; most commonly..."

Abstract line 42 - outsize should be "oversized"

Abstract line 45 "determined compression of heart..." this does not make sense? perhaps you meant "cause compression..."

Entire manuscript: please use a term other than "district" to describe the mediastinum such as compartment or area etc

Manuscript line 71: cataract surgery "work up" not workout, also the patient did not perform an X-ray; an X-ray was performed.

line 75 "seemed to involve"

line 78 "suspected to represent phrenic nerve involvement"

line 89 "the patient resulted completely asymptomatically" - does not make sense, rephrase as "patient was completely asymptomatic"

Line 109 "Most common origin of masses of the anterior mediastinum are represented by thymic tumors....." this sentence is confusing and choppy and not in propery english; needs to be edited.

line 11-113: "in fact, despite the..." again confusing sentence, needs clarification

line 122: "...the most common autoimmune disorder associate to" - should be "associated with"

REPLY: The text has been extensively modified

Reviewer H

Congratulation for the case and its successful management. It is a challenging one based on the tumor size and the phrenic nerve involvement in a MG patient, as well as for the kind of patient.

I only want to make some comments and questions.

1) For me is surprising that a patient with 21 trisomy had no cardiological evaluation in life that could reveal that tumor, as well as no symptoms with a MG confirmed, maybe that both reasons are why the tumor had so big size.

REPLY: Thank you for your consideration. The patient has had a lot of cardiological evaluation during his life, especially in in the childhood and adolescence. Since the absence of symptoms, the patient never had other tests in the previous 5 years. Also the MG was diagnosed only after the diagnosis of mediastinal mass.

Changes in the text: Not required

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2) Why do you think the β2-microglobulin and α-fetoprotein had so high value then? I was expecting a mix thymoma and embryogenic neoplasm according to the laboratory and radiological findings.

REPLY: We agree with the reviewer, in fact our first suspect was a germ cell tumor. Our pathologist, however, did not find embryogenic neoplasm cell in the specimen. Unfortunately, we don't have an explanation for this finding (patient, moreover, was not suffering from hepatitis) as well as there is no literature in this regard.
Not required

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3) Why did you decide as an approach, sternotomy better than left thoracotomy or a combined one?

REPLY: Thank you for your question. At our center we usually perform a sternotomy approach for almost all the anterior mediastinal masses, especially in case of suspect involvement of the main vessels of the mediastinum in order to get a wider operating field and a major control on the surrounding structures.

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4) Why didn't you perform a left diaphragmatic plication? In patients with MG confirmed and phrenic nerve paralysis should be mandatory.

REPLY: Thank you for your question; usually we don't perform a diaphragmatic plication in asymptomatic patient (especially when phrenic nerve injury is not datable)

but we usually wait at least 6 months after surgery before reconsider a diaphragmatic plication. Nevertheless, in this specific case, the diaphragm had been repaired with not adsorbable sutures both for the diaphragmatic defect and for the intraoperative finding of left congenital hernia. The text has been modified to better clarify this aspect.

Thank you for sharing the case and congratulations for the results.