Author's response to reviews

Title: Incidental advanced-stage Hodgkin’s lymphoma diagnosed at the time of radical prostatectomy for prostatic cancer: a case report and review of literature.

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Author's response to reviews: see over
Dear Editor,

thank you for returning to us our manuscript entitled “Incidental advanced-stage Hodgkin’s lymphoma diagnosed at the time of radical prostatectomy for prostatic cancer: a case report and review of literature.”

Enclosed please find the revised version. Indeed, we have revised the manuscript addressing the comments of the editor in consideration of the points raised by the reviewers, and, as requested, provided a point-by-point response to the concerns.

Comment 1:

“Suggest careful proofreading. Multiple syntax and diction errors. English language editing service recommended”

Authors’ response:

We submitted our manuscript to a native English-speaking reviewer who made some changes to the English Language structure and syntax.

Comment 2:

“Please state the patient's PSA doubling time just prior to the initiation of ADT”

Authors’ response:

Patient was referred to Our Institution after having been operated on at another Centre, with postsurgical PSA values of 0.34 ng/mL (this dosage was performed one month after surgery), thus showing “biochemical residual” of disease. A second PSA dosage was performed in course of administration of chemotherapy for HL, already demonstrating a biochemical progression of disease (PSA value was 0.71 ng/mL), and further confirmed by another dosage performed after four additional weeks (PSA value at that time: 0.96 ng/mL). Estimated PSA doubling time prior to initiation of androgen-deprivation therapy was therefore 1.92 months.

PSA doubling time was added, as requested, to line 110 of the case presentation section.
Comment 3:

“How did the multidisciplinary panel conclude that stage IV HL was more aggressive than high-volume Gleason 10 PCa? What is the actuarial disease specific survival of these malignancies in terms of 1) natural history (‘untreated’) and 2) after aggressive gold-standard therapy?”

Authors’ response:

As we described in the report, patient was referred to our Institution with a biochemical persistence of PCa only, after he had already undergone radical retropubic prostatectomy, during which the diagnosis of HL was made on sampled pelvic lymph nodes. A complete re-staging was performed after the patient came to our attention and, at that time, the only radiological evidences were multiple lymphadenopathies on both sides of the diaphragm, and an enhanced metabolic activity in the spleen and skeleton. This findings were consistent with a diagnosis of diffused HL, either in consideration of site of disease or of the type of diagnostic technique used (namely FDG-PET), also considering that PSA level was 0.34 ng/mL. Hence, we could assume that the hematologic neoplasm was to consider as a stage IV disease, while there was only a biochemical evidence of PCa, as highlighted by the post-surgical PSA level, although (as we already stated at lines 100-101) “in principle, bone involvement from PCa could not be completely excluded”.

Patient presenting with only a local persistence of PCa after radical surgery, may benefit from salvage radiation therapy, which is associated with a significant increase in prostate cancer-specific survival relative to those who receive no salvage treatment, independent of other prognostic features such as pathological stage or Gleason’s score. [Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, Walsh PC. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA. 2008 Jun 18;299(23):2760-9. doi: 10.1001/jama.299.23.2760. PubMed PMID: 18560003; PubMed Central PMCID: PMC3076799.]

Nevertheless, there is no shared consensus about the timing of the administration of radiation therapy after surgery, also in view of the potential urologic side effects of this treatment which may worsen those coming from surgery itself. Moreover, in consideration of a rising value of PSA, we started a hormonal therapy, which is demonstrated to be “able to prolong time to metastatization and probably PCa-specific survival [references 22, 23]” (lines 241-242 of the manuscript).
The prognosis for patients with Hodgkin’s lymphoma has steadily improved in the last 50 years, and cure is expected for the great majority of patients, irrespective of stage. Untreated advanced-stage HL (referred to as stage III-IV in literature) is a reliably fatal condition in most cases, while 5-year survival rates after aggressive gold-standard treatment ranges from 88% (for ABVD regimen) to 95% (for BEACOPP escalated regimen). [Skoetz N, Trelle S, Rancea M, Haverkamp H, Diehl V, Engert A, Borchmann P. Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: a systematic review and network meta-analysis. Lancet Oncol. 2013 Sep;14(10):943-52. doi: 10.1016/S1470-2045(13)70341-3. Epub 2013 Aug 13. Review. PubMed PMID: 23948348.]

As we have already stated in the original version of the manuscript, we considered the hematologic neoplasm as the most aggressive condition between the two, as long as it was likely it may have quickly progressed and become in short term life-threatening for the patient, if untreated. On these premises and in name of high cure rates for HL, we deemed that it deserved an immediate gold-standard treatment.

On the other hand, we were just facing a “biochemical disease”, and this allowed us to postpone the salvage radiation treatment on the pelvis, taking also advantage from the response to hormonal therapy, which was initiated in the meanwhile.

These information had already been added to the discussion section of the original manuscript, each one supplied with the appropriate references.

Comment 4:

- “This case report is poorly organized. It needs to become much more succinct. If this is to become an useful contribution the literature, it should roughly be organized as follows: Here we describe the multidisciplinary management of a patient with Gleason 10 PCa who was found to have incidental Stage IV HL after RP. Workup after pathological LN examination included _____”

Authors’ response:

As suggested, the case presentation section was re-arranged and shortened, following the given advices.
- “Due to the need for adjuvant PCa-targeted treatment, a multidisciplinary strategy was constructed in order to define the optimal treatment of both HL and PCa. Describe rationale for treating HL first and patient course”

Authors’ response:

Please see authors’ response to comment 3.

Furthermore, we fear that the reviewer missed that at the time the therapeutic decision was made, there was already an evidence of biochemical persistence of PCa. Hence, there was no indication for any “adjuvant PCa-targeted treatment”, but the patient was rather eligible for salvage radiation therapy in addition to hormonal therapy.

- “In the discussion, state what is the rate of incidental hematologic malignancies discovered on pathologic LN exam after RP”

Authors’ response:

As we already stated in our manuscript (lines 146-149), in the available series the overall rate of hematologic malignancies discovered on pathologic LN exam after RP ranges between 0.003% and 1.2%.

In addition, in order to help the reader avoid misinterpretations, in the present version of the manuscript we refer to “hematologic malignancies (HM)” rather than broadly to “second neoplasms”, at line 146.

- “State indications for bone scan and axial imaging pre-op at your center. State what the preferred diagnostic/treatment strategy would have been if the patient had undergone bone scan and axial imaging pre-operatively.”

Authors’ response:

According to the latest Guidelines from the Italian Association for Medical Oncology (AIOM), a patient like the one described by us should have been considered as a “high-risk” patient at disease presentation (e.g. in view of his biopsy Gleason’s score of 10), and therefore eligible for complete bone scan and complete evaluation of the abdomen/pelvis pre-operatively.

According to us, it would become too much speculative and of limited interest to discuss on the hypothetical algorithm that we would have followed in case the patient had undergone an
appropriate work-up before surgery. Furthermore, we already briefly mentioned the issue of the correct evaluation of nodal status in the pre-operative setting using standard imaging techniques (lines 150-157). Eventually, in the discussion section, we examined in depth the challenges encountered in the management of this case, which partly came from an incomplete pre-surgical staging.

-“Shorten your discussion of CD44. It does not need 9 paragraphs--1 paragraph at most. i.e.: “CD44 has been found to be expressed in HL and normal prostate epithelium but not neoplastic/metastatic prostate adenocarcinoma. Consistent with this, CD44 staining in our case showed....”

Authors’ response:

According to the reviewer’s suggestion, we shortened our discussion about CD44, providing a brief summary of the currently available evidences about this molecule in PCa and lymphomas, the results coming from CD44 staining in our case, and the interpretation we gave to these data. At the same time, though we reduced it in terms of length, we tried not to deplete the original intention and meaning of this section of the discussion.

Moreover, during the final revision of the text, some sentences have been minimally refined, without changes in original meaning. Anyway, again, we are ready to make additional changes should it be deemed necessary by the Editor.

We thank you in advance for the consideration and we look forward to hearing soon about the final destiny of our manuscript.

With best regards,

Antonio Di Meglio, MD