Author’s response to reviews

Title: A case of Ewing's sarcoma in a patient with a diagnostic dilemma: a case report and review of literature

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Author’s response to reviews: see over
Reviewer's report

Title: A case of Ewing's sarcoma in a patient with a diagnostic dilemma: a case report and review of literature

Version: 1 Date: 26 June 2015

Reviewer: Elif Meseci

1. Which of the following best describes what type of case report this is?: Unexpected or unusual presentations of a disease

2. Do you believe the case report is authentic?: Yes

3. Do you have any ethical concerns?: No Is the Abstract representative of the case presented?: Yes

4. Does the Introduction explain the relevance of the case to the medical literature?: Yes

5. Does the article report relevant patient information?: Yes

6. Does the article report relevant physical examination findings?: Yes

7. Does the article report important dates and times in this case?: Yes

8. Does the article report the diagnostic assessments?: Yes

9. Does the article report the types of intervention?: Yes

10. Does the article report a summary of the clinical course of all follow-up visits?: Yes

11. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?: Yes

12. Does the case represent a useful contribution to the medical literature?: Yes, it deserves to publish

13. Was written informed consent to publish this case obtained?: Yes

14. Is the anonymity of the patient protected?: Yes

15. Additional comments to authors?: If the patient had parametrial and vaginal involvement, then why they didn't do radical hysterectomy and pelvic lymphadenectomy? They should give information about residue tumor and the surgical specimen like were there any involvement on the surgical margins? or any other focus?

1. Patient was referred to a tertiary care center for surgery, once Ewing’s diagnosis was confirmed. They did not perform pelvic lymph node dissection for unclear reasons.

2. The following statement now appears from line 18 to 21 under case presentation.

   “patient underwent total hysterectomy and bilateral salpingo-oophorectomy, upper vaginectomy, and resection of parametrium. Surgical pathology showed stage IIB Ewing’s sarcoma involving the cervix and extending into right parametrium. Endometrium, ovaries and fallopian tubes were unremarkable. Margins were free of tumor.”

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable Declaration of competing interests: I declare that I have no competing interest
Reviewer's report

Title: A case of Ewing's sarcoma in a patient with a diagnostic dilemma: a case report and review of literature

Version: 1 Date: 24 August 2015

Reviewer: DIVYA KHOSLA

1. Which of the following best describes what type of case report this is?: Unexpected or unusual presentations of a disease

2. Do you believe the case report is authentic?: The case report is authentic. But the treatment part needs to be elaborated more. The manuscript requires major compulsory revisions.

Please see below for changes to parts of the article

3. Do you have any ethical concerns?: I don’t have any ethical concerns

4. Is the Abstract representative of the case presented?: Abstract needs to be modified a bit. The treatment part should be rewritten for better clarity. The stage of disease should be mentioned. Stage is very important as it will guide whether the disease is resectable or not. Also in case presentation, it’s been mentioned that there was involvement of vagina and parametrium on MRI. Was the disease completely resected?

   a. Stage of the disease has been added. The following statement now appears at the end of case presentation in abstract.

      “The patient underwent surgery which confirmed stage IIB Ewing’s sarcoma.”

   b. The following statement has been added to case presentation from line 18 to 21

      “Patient underwent total hysterectomy and bilateral salpingo-oophorectomy, upper vaginectomy, and resection of parametrium. Surgical pathology showed stage IIB Ewing’s sarcoma involving the cervix and extending into right parametrium. Endometrium, ovaries and fallopian tubes were unremarkable. Margins were free of tumor.”

2. In case presentation, it has been mentioned that subsequently chemotherapy was discontinued and patient was taken up for surgery.... What was the dose of radiation planned and what was delivered? Whether patient showed any response to chemoradiation?

   The following statement has been added to case presentation from line 10 to 12

   “She completed two cycles of Cisplatin, Etoposide and the planned course of 5040cGy over 28 fractions of 180cGy each, which led to resolution of vaginal Bleeding.”

5. Does the Introduction explain the relevance of the case to the medical literature?: Yes. But appropriate references should be added. To Write the last line in introduction as .... “In this article, we present a case of primary PNET tumor of the cervix which is a rare entity and can lead to diagnostic dilemma. It was initially diagnosed as neuroendocrine small cell carcinoma of the cervix. We also summarize.....”

   a. Reference has been added as advised

   b. The above referenced statement has been added to Introduction as follows

      “In this article, we present a case of primary PNET tumor of the cervix which is a rare entity and can lead to a diagnostic dilemma. It was initially diagnosed as neuroendocrine small cell carcinoma of the cervix. We also summarize a literature review of all the cases reported in the English language.”

6. Does the article report relevant patient information?: Yes

7. Does the article report relevant physical examination findings?: Yes
8. Does the article report important dates and times in this case?: Yes
9. Does the article report the diagnostic assessments?: Yes
10. Does the article report the types of intervention?: Yes
11. Does the article report a summary of the clinical course of all follow-up visits?: No
12. If any information is missing from the reporting, please detail it here.: Clinical course of follow-up visits
   The following statements have been added to case presentation
   “She was started on chemotherapy with VAC (vincristine 2mg/m2 day 1, Adriamycin 75mg/m2, cyclophosphamide with MESNA 1200mg/m2 day 1), alternating with IE (Ifosfamide plus MESNA 1800mg/m2 days 1-5, and Etoposide 100mg/m2) every three weeks. PET scan done after two cycles was negative for recurrence of tumor. After four cycles, nine months from initial diagnosis, she developed acute renal failure. CT scans showed evidence of metastases to lumbar spine, pelvis and bladder. Nephrostomy tubes were placed which improved renal function. Two weeks later she presented with distal colonic obstruction secondary to extensive pelvic tumor. Exploratory laparotomy and diverting loop colostomy were done. One week later her disease progressed with new lung metastases, which led to clinical deterioration and death with an overall survival of 10 months.”
13. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?: Discussion needs to be shortened. It needs major revision Conclusion should come after discussion
   Discussion has been shortened with changes to include Stage, radiation therapy and chemotherapy doses and schedule, duration of follow up, time frame for development of metastasis and sites of metastases have been included. References have been updated. Discussion now comes prior to conclusion.
14. Does the case represent a useful contribution to the medical literature?: The case can be published provided the queries have been addressed and revision has been done. It is a rare entity and should be reported.
   All the queries have been addressed
15. Was written informed consent to publish this case obtained?: Yes
16. Is the anonymity of the patient protected?: Yes
17. Additional comments to authors?:
   Manuscript title
   A case of Ewing’s sarcoma in a patient with a diagnostic dilemma: a case report and review of literature
   Comments: The manuscript needs major revision. Also needs language corrections before being published.
   Revision has been made with all the changes suggested.
   Abstract
   1. Mention the stage of disease. Stage is very important as it will guide whether the disease is resectable or not. Also in case presentation, it’s been mentioned that there was involvement of vagina and parametrium on MRI. Was the disease completely resected?
      a. Stage of the disease has been added.
      b. The following statement now appears at the end of case presentation in abstract.
         “The patient underwent surgery which confirmed stage IIB Ewing’s sarcoma.”
      c. The following statement has been added to case presentation from line 18 to 21
         “patient underwent total hysterectomy and bilateral salpingo-oophorectomy, upper vaginectomy, and resection of parametrium. Surgical pathology showed stage IIB Ewing’s sarcoma involving the cervix and extending into right parametrium. Endometrium, ovaries and fallopian tubes were unremarkable. Margins were free of tumor.”
2. In case presentation, it has been mentioned that subsequently chemotherapy was discontinued and patient was taken up for surgery. What was the dose of radiation planned and what was delivered? Whether patient showed any response to chemoradiation?

_The following statement has been added to case presentation from line 10 to 12_

“She completed two cycles of Cisplatin, Etoposide and the planned course of 5040cGy over 28 fractions of 180cGy each, which led to resolution of vaginal Bleeding.”

_The following statement has been added to Introduction as follows_

“In this article, we present a case of primary PNET tumor of the cervix which is a rare entity and can lead to a diagnostic dilemma. It was initially diagnosed as neuroendocrine small cell carcinoma of the cervix. We also summarize a literature review of all the cases reported in the English language.”

_The following statement has been added to Case Presentation at line 19_

“Surgical pathology showed stage IIB Ewing’s sarcoma involving the cervix and extending into right parametrium.”

_The following statement has been added to Case Presentation from line 10 to 12_

“She completed two cycles of Cisplatin, Etoposide and the planned course of 5040cGy over 28 fractions of 180cGy each, which led to resolution of vaginal Bleeding.”

_The following statement has been added to case presentation at line 19_

“Surgical pathology showed stage IIB Ewing’s sarcoma involving the cervix and extending into right parametrium. Endometrium, ovaries and fallopian tubes were unremarkable. Margins were free of tumor.”

_The following statement has been added to case presentation_

“She was started on chemotherapy with VAC (vincristine 2mg/m2 day 1, Adriamycin 75mg/m2, cyclophosphamide with MESNA 1200mg/m2 day 1), alternating with IE (Ifosfamide plus MESNA 1800mg/m2 days 1-5, and Etoposide 100mg/m2) every three weeks.
The following statement has been added to case presentation

After four cycles, nine months from initial diagnosis, she developed acute renal failure.

5. After what duration of follow-up, patient developed metastasis and what was the site of metastasis?

The following statement has been added to case presentation

“After four cycles, nine months from initial diagnosis, she developed acute renal failure. CT scans showed evidence of metastases to lumbar spine, pelvis and bladder. Nephrostomy tubes were placed which improved renal function. Two weeks later she presented with distal colonic obstruction secondary to extensive pelvic tumor. Exploratory laparotomy and diverting loop colostomy were done. One week later her disease progressed with new lung metastases, which led to clinical deterioration and death with an overall survival of 10 months.”

6. Conclusion should come after discussion

As per the article submission guidelines of the journal, the abstract did require a conclusion, hence a brief conclusion ended up before the discussion. The article also has a conclusion at the end of discussion.

Discussion

1. Discussion needs to be shortened. Discussion has been shortened

2. After first line mention the references numbers and also write in the table corresponding to author’s name.

References have been added in the table next to the corresponding author’s name

3. Please add references numerically in serial order in the text. References have been added numerically in the text.

4. Delete the line... “We noted a bimodal peak, with tumors either presenting in adolescence or perimenopausal period”.

The line “we noted a bimodal peak………..”.has been deleted as recommended by the reviewer.

5. Mention the references in the following lines “The vaginal bleeding with enlarged uterus led to the preliminary diagnosis of fibroid in two patients. One patient had vaginal stenosis and necrotic tissue on the cervix.”

The recommended references have been included.

6. It would be better if stage is mentioned in number along with percentage in bracket. Write how many patients presented in stage I B, IIA, IIB, IIIA, IIIB, IV and then correlate the outcome with stage.

a. The following statement has been added to paragraph 3 in discussion.

“Stage was not reported in three cases. Ten (62.5%) patients were stage IB1 or IB2, one (6.25%) stage IIA, two (12.5%) stage II B, one (6.25%) stage IIIB and two stage IV (12.5%).”

b. The outcome correlation to stage has been added to the treatment section as below.

“Similar to skeletal Ewing’s sarcoma, the most unfavorable prognostic factor is the presence of distant metastasis, with stage IV disease being universally fatal.”

7. The following sentence needs to be revised....This is encouraging, as early stage at diagnosis, is a good prognostic factor per our literature review.

The following statement has been added to paragraph 6 in treatment

“Similar to skeletal Ewing’s sarcoma, the most unfavorable prognostic factor is the presence of distant metastasis, with stage IV disease being universally fatal.”

8. It would be better if you write how PET is helpful in diagnosis and management. It was done in other case report also. Better not to write that it was done only in our case.

The following statement has been added to paragraph 4 in discussion

“Our review shows that PNET tumors are highly FDG avid. PET scan may be a useful imaging modality in diagnosis, staging and monitoring response to therapy.”

9. The paragraph on CA-125 should be deleted. Paragraph on CA-125 has been deleted.
10. References should be mentioned in serial order in the entire article. References have been adjusted in serial order in the entire article.

11. Rewrite the following line......The only of cervical PNET that was initially misdiagnosed as lymphoma, was reported by Benbrahim et al (2). The sentence has been rewritten as suggested by the reviewer as follows “Benbrahim et al reported a case of cervical PNET that was initially misdiagnosed as lymphoma.”

12. Mention references in the following lines...... Cytogenetic analysis was done in three cases. FISH was used in two cases while RT-PCR was used in two cases. References for cytogenetics, FISH and RT-PCR have been included.

13. Write as ....Currently there is no uniformity of treatment, because of the rarity of this neoplasm. Sentence has been edited as suggested

14. Better write it as Snijders-Keilholz et al. Recommended.... Sentence has been edited as suggested and it appears as follows in the 1st paragraph of treatment “Snijders- Keilholz et al. recommended a multidisciplinary approach similar to that used in osseous PNETs with induction chemotherapy, surgery, adjuvant chemotherapy and radiation.”

15. Rather writing it most of the patients, mention how many patients underwent LND out of 18 reported in the literature and what is the role of LND in PNET of uterine cervix The following statements have been added to paragraph 2 of treatment “Pelvic lymph node dissection was performed in eleven out of nineteen cases. Of these eleven cases, eight patients are alive without recurrence, the outcome of two cases is unknown and one patient died from metastatic disease four years later. Of the eight cases that did not have lymph node dissection, two were inoperable due to stage IIIB5 and IV16 disease. The stage of one patient is unknown. Remaining five cases were early stage (three stage I B2, two stage II B). Of these five cases, one did not receive any chemotherapy and died at four years. Our patient (stage IIB) died at ten months despite chemotherapy and radiation. The other three cases received chemotherapy and are alive without relapse. The contribution of PLND to overall survival, especially in patients that had chemoradiation is unclear.”

16. There is lot of repetition such as one case reported by.... Modify the lines so that they dont look monotonous. Paper has been edited to avoid monotony.

17. In paragraph on radiation therapy, discuss how many patients received radiation therapy and what was the intent: definitive, adjuvant or palliative. Mention the dose and dose fractionation used with median dose. Also report how many patients developed local recurrence. The following statements have been added to paragraph 4 of treatment “Eight of nineteen patients (Table 1) received radiation therapy. The intent of radiation was palliative in one case, definitive in three, and adjuvant in four. The definitive chemoradiation given in our patient was part of small cell carcinoma regimen due to an initial small cell diagnosis, but she subsequently developed pelvic recurrence nine months after diagnosis. Another case death from pelvic recurrence nine months after diagnosis was reported by Xiao et.al,18 but the authors did not report if radiation was given. Radiation doses ranged from 40-55 gray with the fractionation schedule of 180-200 Cgy over 4-5 weeks. Overall we conclude that adjuvant radiation may have a role in preventing local recurrence and should be considered when appropriate.”

18. Baldini et al... Add reference and reference number in the manuscript. Baldini etal ... reference has been added to manuscript and reference list

19. Write conclusion after discussion. Conclusion has been written after discussion, however, the abstract also has a brief conclusion as the article guidelines required a conclusion in the abstract section also.
20. Submit MRI images of better quality. *MRI images of better quality have been submitted*

21. Write full forms of abbreviations used in the table below it.

*Full forms of abbreviations have been mentioned under the table*

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Declaration of competing interests:** I have no conflicts of interest.