Clinical Case Report

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Case report on the role of radiofrequency-assisted spleen-preserving surgery for splenic metastasis in the era of check-point inhibitors

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Abstract

Rationale: An isolated splenic metastasis is a rare phenomenon noted in advanced stage melanoma. We report the role of radiofrequency (RF) -based splenic-preserving splenectomy in a patient with a solitary splenic metastasis from advanced stage melanoma that was managed with checkpoint inhibitors.

Patient concerns: We report a case of a 60-year-old man who presented with multiple lung metastases and a solitary splenic metastasis with advanced stage melanoma following excision of primary from his trunk 2.3 years back.

Diagnosis: Considering the diagnosis of advanced stage melanoma with multiple lung metastases and a solitary splenic metastasis, and its ongoing progressive nature. This case was discussed in the tumour board meeting.

Interventions: A decision was made to commence treatment with immunotherapy in the form of PD-1 inhibitor (programmed cell death 1 receptor) pembrolizumab. Follow-up restaging computer tomography (CT) scan of the abdomen and chest showed a significant reduction in the lung and chest wall lesions, but the splenic lesion remained unchanged. Given the lack of response to treatment in the splenic metastasis and the significant decrease in lung metastases, the multidisciplinary team decided that a partial splenectomy combined with continued immunotherapy treatment would be appropriate as the success of immunotherapy was imminent within the splenic preservation.

Outcomes: The postoperative recovery was smooth and the patient was discharged from hospital on the sixth postoperative day with normal platelets and white blood cells. The histopathological analysis of the resected specimen showed a metastatic melanoma with negative margins.

At 10-month follow-up after the splenic resection the patient had not experienced further tumour recurrences.

Lessons: Spleen-preserving resection for an isolated, solitary splenic metastasis of melanoma is a feasible approach as it not only preserves the ongoing efficacy of checkpoint inhibitors by preserving the physiological T cell milieu, but the immunomodulation properties of RF can produce potentially additional therapeutic benefit.

Abbreviations: anti-CTLA4 = anticytotoxic T-lymphocyte-associated protein 4, anti-PD-1 = antiprogrammed cell death protein 1, anti-PD-L1 = antiprogrammed cell death-ligand 1, BRAF = B-Raf protein kinase, CT = computer tomography, MEK = mitogen-activated extracellular signal regulated kinase, PD-1 = programmed cell death 1 receptor, RF = radiofrequency.

Keywords: melanoma, radiofrequency, splenic metastasis

1. Introduction

The management of metastatic melanoma has improved considerably in recent years with the introduction of immune checkpoint blockade drugs (anti-CTLA4: anticytotoxic T-lymphocyte-associated protein 4; anti-PD-1: antiprogrammed cell death protein 1; and anti-PD-L1: antiprogrammed cell death-ligand 1) and targeted therapy, such as BRAF (B-Raf protein kinase) and MEK (mitogen-activated extracellular signal regulated kinase) inhibitors.[1,2]

The programmed cell death 1 receptor (PD-1), an inhibitory receptor present on the activated T cells, binds to its ligand (PD-L1) present on the tumor cells and downregulates the activated T cell to produce an effective immune response.[3] Thus antibodies directed against PD-1 (nivolumab, pembrolizumab) or the PD-L1 ligand may restore or augment the antitumor immune response making it able to suppress the cancerous melanoma cells.[4–6]

Metastasis to the spleen is considered as a rare event and marks the terminal end of the spectrum of melanoma disease processes. Recently, the reported incidence of splenic metastasis has increased owing to the improvement in medical imaging and the long-term follow-up of patients with melanoma.[7–10] There are no specific

Editor: Goran Augustin.

Consent: Written informed consent to publication was obtained from the patient.

Conflicts of interest: Prof. Habib Nagy has shares and a directorship in a company, EMcision Limited, that developed the Habib 4X. Since 2005 the Habib 4X has been manufactured, marketed, and sold by AngioDynamics, Inc., USA. None of the other contributing authors has any conflict of interest to declare including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Medicine (2017) 96:49(e9106)

Received: 29 June 2017 / Received in final form: 13 November 2017 / Accepted: 14 November 2017

http://dx.doi.org/10.1097/MD.0000000000009106

guidelines regarding the management of such advanced staged melanoma patients. Nevertheless, many case reports in the literature suggest improved survival following surgical resection. The surgical procedure in the form of open or laparoscopic splenectomy seems a realistic and reasonable therapeutic option.[11,12]

However, considering the success of checkpoint inhibitors and the availability of a radiofrequency (RF) device to assist with the surgery allows partial splenectomy to be offered as a therapeutic option. The rationale behind RF-based splenectomy is self-explanatory in terms of maintenance of immunological benefits of immunotherapy through the preservation of spleen. Together with that, post RF ablative changes in the immune system have been considered as evidence for both a systemic and local immunomodulatory effect.[13–15] Furthermore, the immunomodulatory effects of RF could be potentially beneficial in the augmentation of therapeutic effects of checkpoint inhibitors.[16,17] Immunologically, splenectomy is associated with loss of memory B cells which are preserved in the case of a partial splenectomy, where the number of T and B lymphocytes increase as do the number of monocytes in the red pulp.[18–20]

Here, we report the role of RF-based splenic-preserving splenectomy in a patient with a solitary splenic metastasis in advanced stage melanoma that was managed with checkpoint inhibitors.

2. Case report

2.1. Case presentation

A 60-year-old male patient presented to our institute for the management of a solitary splenic metastasis. The patient was diagnosed with melanoma following excision of a nevus from his trunk and sentinel lymph node biopsy in November 2014. The primary histopathological assessment revealed a Breslow thickness of 1.8 mm, Stage T2 lesion with tumor-free margin and no lymph node metastasis. The patient was doing well until May 2015 when a follow-up CT scan revealed 2 indeterminate subcentimetric lung lesions in the lower left lobe.

He remained asymptomatic until October 2015 when he developed a suspicious lesion on his trunk. Following a wide local excision and histopathological assessment the lesion was reported as a T1 lesion of a Breslow thickness of 0.6 mm with tumor-free margins.

The repeat follow-up CT scan in November 2015 showed development of an enlarged suspicious right axillary lymph node. An ultrasound-guided biopsy confirmed this as a metastatic lymph node secondary to melanoma. In the presence of this diagnosis a right axillary lymphadenectomy was completed.

The patient remained asymptomatic until February 2016 when he developed sepsis and cellulitis at the site of lymphadenectomy. He was managed successfully with incision and drainage and administration of parenteral antibiotics. At the next follow-up CT scan 3 new lung lesions in the chest wall were reported, although no change was noted in earlier lesions seen in the right lung.

In presence of progressive disease, the decision was made to start immunotherapy a PD-1 inhibitor, pembrolizumab (10 mg/kg/every 3 weeks intravenously), in June 2016. The subsequent follow-up scan in August 2016 showed a new solitary metastatic lesion in the spleen. He was maintained on the pembrolizumab, and follow-up restaging CT scan performed in November 2016 revealed a significant reduction in the lung and chest wall lesions, but the splenic lesion remained unchanged (Fig. 1). The pembrolizumab treatment was well tolerated, and the performance status of patient improved; however, he developed an adverse effect of treatment as extensive changes in the lung compatible with fibrosis was revealed on imaging. This was suggestive of a diagnosis of immune-related pneumonitis, which improved with stopping the pembrolizumab and giving oral prednisolone. The pembrolizumab was reintroduced following resolution of pneumonitis.

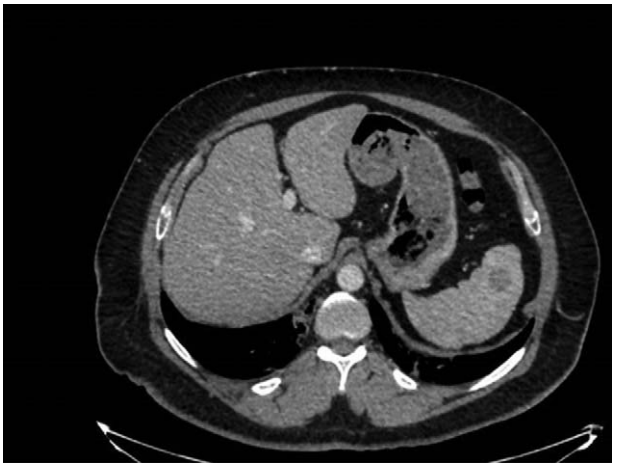

Figure 1. Axial CT scan shows a hypodense lesion in the spleen.

In view of the nonresponse to treatment of the splenic metastasis, the multidisciplinary team evaluated the available options and decided to advise partial splenectomy with continued immunotherapy as the success of immunotherapy was inherent with spleen preservation.

The RF-based splenic resection was performed at the end of December.

2.2. Surgical technique

Following informed consent, the patient was placed in the left lateral position under general anesthesia, and a left subcostal incision was made. There were no other pathological lesions noted. The dissection was performed along the avascular peritoneal attachments such as splenocolic and lienorenal

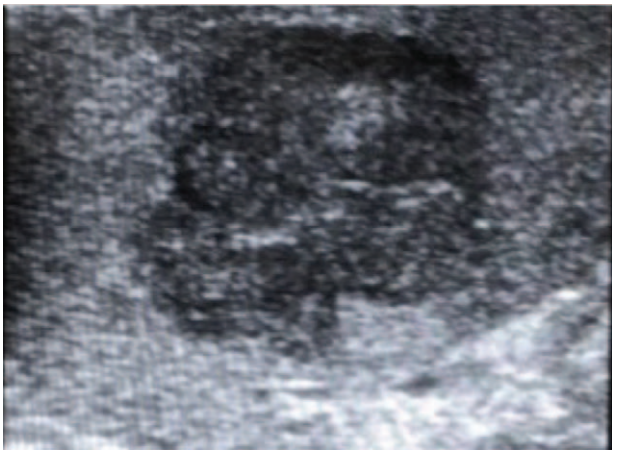

Figure 2. Intraoperative sonogram shows hypoechoic lesion in the spleen.

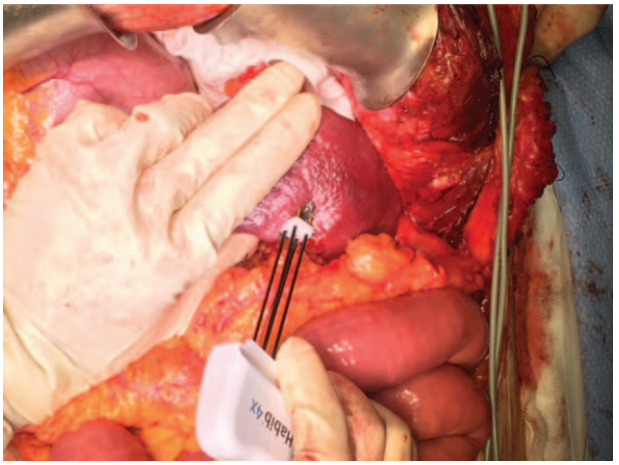

Figure 3. Sequential application of the RF probe (Habib 4X) to create parallel ablation lines 1 cm adjacent to tumor.

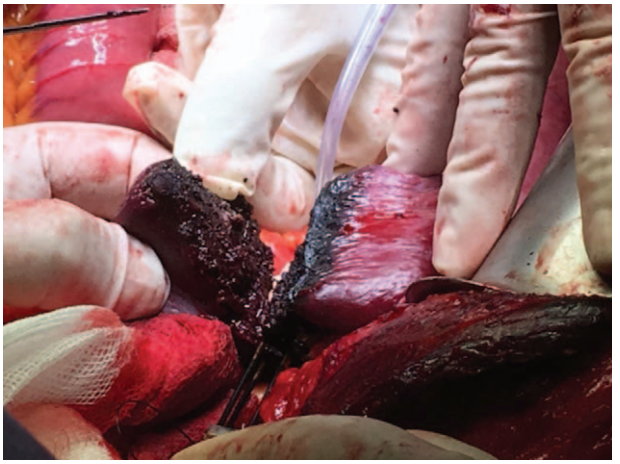

Figure 5. Resection at proximal margin of 12 to 14 mm width necrotic splenic parenchyma adjacent to tumor (Note: 10 mm of extra-safety margin at the resection margin).

ligament around the spleen and the short gastric vessels were ligated in the gastrosplenic ligament. The spleen was gently grasped and displaced medially toward the incision area, and the site and size of the tumor were confirmed with intraoperative ultrasound (Fig. 2). The resection margin was marked with argon diathermy. The aim was to use the 4-needle RF probe to ablate a plane of resection to achieve a 2 cm resection margin away from the tumor. In this technique, parallel lines of ablation were created by the sequential application of RF-based device, Habib 4X (AngioDynamics, Inc., New York, NJ) by using the a RF generator at 60 W for optimal splenic parenchymal coagulation. The first ablation line was performed 1 cm from the tumor, and then a second parallel line made between the first line and the tumor edge (Fig. 3). Several transverse applications were required to create a third line which connected the vertical parallel lines and ensured complete ablation (Fig. 4). The probe was moved swiftly in a see-saw fashion over 3 to 5 mm of its axis. The movement of the probe helped to avoid any adherence of the splenic tissue to the needles. The Habib 4X device effectively created a 1 cm thick area of ablated and coagulated tumor-free margin. The resection was performed with a scalpel dividing the parenchyma close to the first coagulated edge next to the tumor, leaving ~10 mm of coagulated splenic parenchyma (Figs. 5 and 6). At the end of the resection, the device was used to arrest any residual bleeding at the resection margin. The postoperative recovery was smooth and the patient was discharged on the sixth postoperative day with normal platelets and white blood cells. The histopathology of the resected specimen revealed a metastatic melanoma 26 mm in the maximum diameter. At 10-month follow-up after the splenic resection, the patient was well and without tumor recurrences.

3. Discussion

Splenic metastasis is part of the advanced multivisceral metastatic melanoma disease process. An incidental diagnosis of splenic metastasis has been made on imaging performed for other reasons or autopsy.[21–23]

There are many case reports present in the literature which suggest splenectomy as a therapeutic option. However, due to the recent success and reported improved survival following the inception of immune checkpoint blockade drugs (anti-CTLA4,

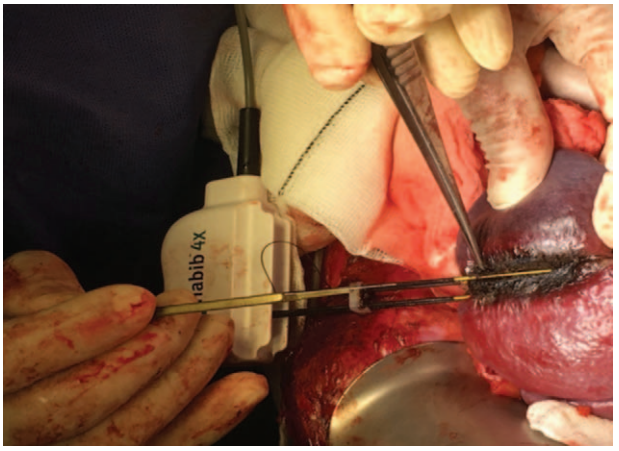

Figure 4. Sequential application of the RF probe to create transverse ablation lines which connected to the parallel lines of ablation.

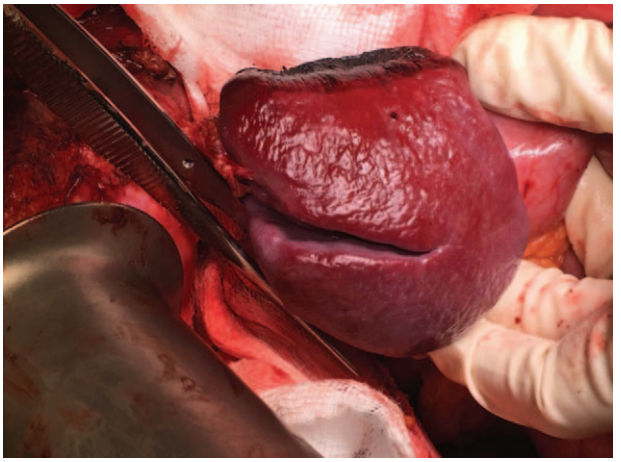

Figure 6. Residual in situ spleen postpartial splenectomy.

anti-PD-1, and anti-PD-L1) there is emerging evidence toward the role of splenic preservation. The PD-1 receptor is an inhibitory receptor found on activated T cells.[24–26] The ability of the activated T cell to produce an effective immune response is downregulated when PD-1 binds to its ligand (PD-L1) present on tumor cells. The introduction of antibodies directed against PD-1 (nivolumab, pembrolizumab) or the PD-1 ligand may reinstate an antitumor immune response by T cells to suppress the melanoma cells.[27,28] Hence, the effectiveness of these drugs is dependent on T cell populations together with the fact that the spleen plays an important and distinctive role in T cell activation. Thus, any modality which offers spleen preservation would be a more beneficial proposition. Splenic preservation would assist in maintaining the physiological functionality of T cells and as a consequence keep the optimal efficacy of check point inhibitors.[29–35] Our patient in this index report developed pneumonitis, an uncommon complication encountered with an antiprogrammed cell death receptor 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) monoclonal antibody. However, drug-induced pneumonitis is a diagnosis of exclusion, and alternative diagnoses, including infection and malignancy, need to be sought first.[36,37] There have been no prospective clinical trials done so far to outline the management of pneumonitis. However, observational studies suggested an empirical approach in terms of withholding or stopping the drug with corticosteroid treatment in cases of severe disease.[38,39]

The present case highlights the importance of spleen preservation in order to maintain and boost the therapeutic efficacy of immunotherapy, such as PD-1 inhibitors. To the best of our knowledge, this is the first case report where RF-based partial splenectomy has been used as an adjunct to PD-1 inhibitors to control the metastatic melanoma disease process, although this requires further investigation through the randomized clinical trials.

4. Conclusion

The isolated splenic metastasis is a rare phenomenon noted in an advanced stage of the melanoma. The RF-based spleen-preserving resection for isolated, solitary splenic metastasis of melanoma is a feasible approach as it not only preserves the ongoing efficacy of checkpoint inhibitors by preserving the physiological T cell milieu, but combined with the immunomodulation properties of RF can produces potentially additional therapeutic benefit.

Acknowledgment

The authors would like to thank the patient for allowing them to publish the case report and to use the images taken during his hospital admission.

We would like to thank Ms Joanna Nicholls for her help in reviewing and editing this manuscript.

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