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Case Report

Microwave Ablation and Immune Activation in the Treatment of Recurrent Colorectal Lung Metastases: A Case Report

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Abstract
We present a patient with colorectal metastases confined to the lungs and treated with multiple resections until this was not an option anymore, followed by stereotactic body radiation therapy until this option was drained. Then, the patient was successfully treated with multiple microwave ablations combined with immunological activation targeting the programmed cell death 1 receptor (PD-1), possibly instigating a powerful abscopal effect. Techniques, doses, and radiological findings are presented.

Introduction

Colorectal cancer is the third most common cancer worldwide and also the fourth most common cause of cancer-related death [1]. At presentation, staging of the disease is crucial, giving prognostic information and guidance for treatment decision making. Curative treatment is indicated when complete removal is deemed possible. Half of all patients have dis-

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seminated disease at the time of diagnosis or develop evidence of metastatic disease later. Approximately 30% will develop liver metastases [2] and around 20% will develop lung metastases [3, 4], the 2 most common sites for distant metastases. Lung presentation has a better prognosis than other metastatic sites, with a slower disease progression [5]. The first choice is resection with the possibility of further treatment with stereotactic body radiation therapy (SBRT) or thermal ablative techniques as salvage procedures. Guidelines often suggest chemotherapy with response or stable disease before attempting potentially curative treatment of metastatic disease [6]. A completely new area of interest has opened up with the arrival of immunomodulating drugs, but these need targetable antigenic properties on the tumours. This is seen with colorectal cancers that have microsatellite instability in their genome, causing a changing expression of surface antigens allowing cytotoxic T-cell activity that can be unlocked with drugs like programmed cell death 1 receptor (PD-1) action [6, 7]. An alternative method to open new antigens on tumours is local destruction with ablative techniques such as cryotherapy, radiofrequency (RF) ablation, or microwave ablation. Microwaves have the benefit of being able to deliver energy quickly keeping ablation times short and overcoming cooling from adjacent vessels [8, 9]. Also, for lung treatment, there is no need for tissue conductivity as is the case for RF, as microwaves can propagate through the alveolar air. If a good immunological response can be elicited, a general effect on all tumoural tissue can sometimes be noticed, the abscopal effect, which has been shown in animals receiving immunomodulation with local ablative techniques [10].

Case Presentation

We present the case of a 51-year-old woman with a history of Guillain-Barré syndrome as a teenager, probable neuroborreliosis in the 1980s, and a malignant melanoma in situ in the 1990s. She has given informed consent to this report. The patient had repeat rectal surgeries for sphincter damage after childbirth, and in 2011, she was diagnosed with a T4 rectal cancer causing haemorrhage. No distant metastases were found and treatment with curative intent was decided at a multidisciplinary team conference. She had neoadjuvant chemotherapy with fluorouracil and leucovorin followed by radiation with 50.4 Gy to the rectum. The tumour was resected half a year after the diagnosis. The postoperative course was uneventful except for a superficial wound infection and she was discharged after 3 weeks of hospitalization. After 2 weeks, she was readmitted because of a Takotsubo cardiomyopathy and intestinal obstruction requiring more surgery with resection of a short segment of small bowel. After 1 year, the first lung metastases were diagnosed with a 2-cm metastasis in the right lower lobe and a 5-mm. tumour in the lower left lobe. After 3 pulmonary resective procedures, further lung metastases were seen during follow-up. A second line of chemotherapy was started with oxaliplatin, resulting in shrinkage of the noted lesions. Then, local treatment was done with SBRT, 17 Gy ×3 for 2 right-sided metastases and a resection of the left lung, 3 years after the resection of the primary tumour. Three months later a new lung metastasis was diagnosed and treated with SBRT, 7 Gy ×8. Six months later, 2 more lung lesions were found and a third line of chemotherapy based on irinotecan was started, but as tumour progression was observed, treatment was discontinued after 3 months.

Without having the final test result on microsatellite instability in the tumour, it was decided to start PD-1 treatment (this was not within a clinical trial, since the only available trial in Sweden had not opened yet). Further resections were not possible and the given dose of radiation precludes further SBRT. There were a total of 6 confirmed metastases on both

sides after the first 3 doses of pembrolizumab (standard dose with 2 mg/kg every third week). The CT evaluation showed size increase of all lung metastases, but no new lesions. The only side effect was fatigue. This early evaluation did not contradict further therapy, but before continuing with the immunological treatment, local ablative treatment with microwaves was proposed, as this has become a standard treatment for liver tumours, and also evidenced with a growing pile of international publications on treatment of lung lesions [9, 11–13]. The tumours were deemed treatable and were, after 2 more doses of pembrolizumab, done so in 2 sessions 3 weeks apart using a computer-assisted targeting system (CAS-one; Cascination AG, Bern, Switzerland) and microwaves (Angiodynamics) under immobilization of the lungs with high-flow jet ventilation as described in a previous publication [14]. The patient stayed in hospital overnight after the ablations. During the first ablative session, a pneumothorax was caused and a 16F chest tube with suction was placed and removed after clamping the next day. Images of the procedures are shown in Figure 1.

PD-1 treatment was re-started after 2 weeks. After the sixth course of pembrolizumab, the patient felt pain over the liver area, and experienced low appetite and some weight loss. Further investigations showed no signs of liver metastases or damage, but a drop in serum albumin and elevated ESR and CRP. This rise in inflammatory parameters was judged as potential reaction on PD-1 inhibition and treated with betamethasone. For better pain control, amitriptyline was added to the standard analgesic regimen as there could be a neurogenic pain component. After 3 weeks, the seventh dose of pembrolizumab could be given. Two weeks thereafter, the patient experienced weakness of her left lower leg, finger tremors, and numbness on the ulnar side of the right hand. A neurologist ruled out any suspicion of new metastases or any systemic neurological disease. The symptoms were regarded as side effects of pembrolizumab, although mechanistically not fully understood. The dose of corticosteroids was increased and the eighth course of pembrolizumab was given with no worsening of symptoms.

Images from a follow-up computed tomography are shown in Figure 2 where an inflammatory reaction is initially seen with focal lesions, pseudo-tumours, that later disappeared. After 8 months of follow-up, there have been no signs of new or recurrent lung metastases.

Presently, the patient is still suffering from neurological symptoms that in spite of efforts giving higher doses of steroids are not declining. The other complication is upcoming diffuse non-malignant lesions in both lungs, interpreted as either inflammatory or infectious. These findings were accompanied by shortness of breath and difficulties to walk longer distances. Steroid treatment has only partially alleviated the symptoms, as has antibiotic treatment, covering both gram-positive bacteria and *Pneumocystis carinii*. Further investigations are ongoing. As mentioned, the lung metastasis has not recurred, giving her time off antitumoural treatment.

Conclusion

The presented case demonstrates the possibilities of using stereotactically navigated ablation antennas for microwave ablation of multiple lung metastases. Further, it points to possible immunological benefits when combining ablative treatment with immune activation therapy using PD-1 targeting drugs like pembrolizumab, and promising early clinical results have recently been published in a study from China [15]. The combination could

open a completely new set of possibilities in the field of oncology where efforts should be made to ensure in a prospective controlled fashion.

Statement of Ethics

Informed consent has been provided by the patient.

Disclosure Statement

The authors do not have any conflicts of interest.

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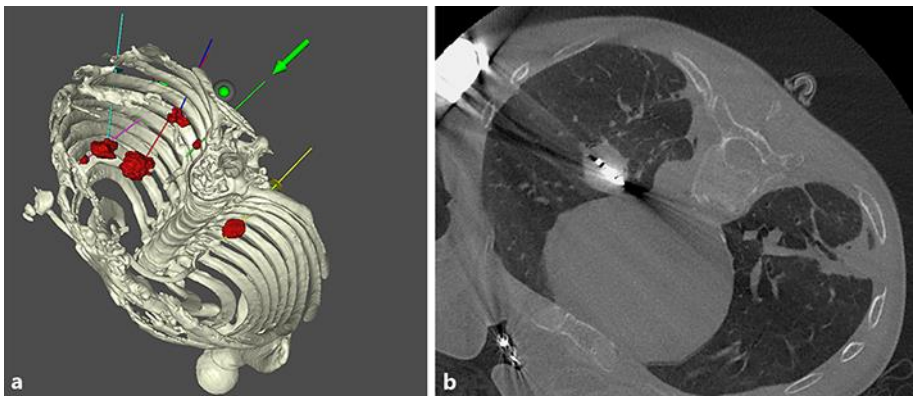

Fig. 1. **a** 3D reconstruction of the ribcage and the 6 metastases with planned trajectories for ablation antennae. View from below, trajectories from dorsal entry. **b** Microwave antenna placed stereotactically within the tumour to be ablated.

Fig. 2. **a** Post-ablation image with multiple small areas with focal reactions, pseudo-tumours, in response to immunotherapy. **b** The same area, 3 months later after treatment with corticosteroids.