

## Histological changes associated with laser interstitial thermal therapy for radiation necrosis: illustrative cases

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**BACKGROUND** Patients with lung cancer and melanoma remain the two largest groups to develop brain metastases. Immunotherapy has been approved for treatment of stage IV disease in both groups. Many of these patients are additionally treated with stereotactic radiosurgery for their brain metastases during ongoing immunotherapy. Use of immunotherapy has been reported to increase the rates of radiation necrosis (RN) after radiosurgery, causing neurological compromise due to growth of the enhancing lesion as well as worsening of associated cerebral edema.

**OBSERVATIONS** Laser interstitial thermal therapy (LITT) is a surgical approach that has been shown effective in the management of RN, especially given its efficacy in early reduction of perilesional edema. However, little remains known about the pathology of the post-LITT lesions and how LITT works in this condition. Here, we present two patients who needed surgical decompression after LITT for RN. Clinical, histopathological, and imaging features of both patients are presented.

**LESSONS** Criteria for selecting the best patients with RN for LITT therapy remains unclear. Given two similarly sized lesions and not too dissimilar clinical histories but with differing outcomes, further investigation is clearly needed to identify predictors of response to LITT in the setting of SRS and immunotherapy-induced RN.

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**KEYWORDS** laser interstitial thermal therapy; radiation necrosis; histological change

Approximately 40%–50% of patients with non-small cell lung cancer (NSCLC) with metastatic disease and up to 70% of patients with melanoma will develop brain metastases.<sup>1–7</sup> First-line treatment of brain metastases for most of these patients will include stereotactic radiosurgery, since its efficacy is well established.<sup>5,6</sup> Best current first-line systemic therapy being offered to melanoma patients is combination anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) and anti-programmed cell death 1 (anti-PD1) immunotherapy, typically using the combination of ipilimumab plus nivolumab.<sup>8–16</sup> Pembrolizumab, an anti-PD1 agent, is used as first-line treatment for NSCLC patients with tumors expressing > 50% programmed cell death ligand 1 (PD-L1). Compared to standard cytotoxic therapy, treatment with immunotherapy has resulted in an improvement in overall survival, progression free survival, objective response rates, and better toxicity profiles.<sup>17,18</sup> Immune checkpoint inhibitors nivolumab,

pembrolizumab and atezolizumab are also approved for patients with advanced NSCLC as first-line agents in combination with chemotherapy in patients whose tumors are PD-L1-positive > 1% but < 50% or alone as second-line agents, while durvalumab is approved as adjuvant treatment after chemotherapy and radiation.<sup>19</sup>

Data regarding safety and efficacy of combined radiation therapy and immunotherapy however remains variable.<sup>20–22</sup> The most common side effect of radiosurgery is radiation necrosis (RN), thought to be an autoreactive response to high-dose radiation injury to the brain surrounding the tumor. Reported RN rates in patients treated with PD-1/PD-L1 inhibitors range from 2.9% to 37.5%.<sup>21–24</sup> Whether these rates are increased compared to when radiosurgery is used in combination with nonimmunotherapy however remains unclear.<sup>21–23,25</sup> Laser interstitial thermal therapy (LITT) is a new technology that has been shown to be

**ABBREVIATIONS** anti-CTLA4 = anti-cytotoxic T-lymphocyte-associated protein 4; anti-PD1 = anti-programmed cell death 1; LITT = laser interstitial thermal therapy; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1; RN = radiation necrosis; SRS = stereotactic radiosurgery.

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effective in the treatment of biopsy-proven RN resulting in resolution of edema and mass effect in the majority of cases.<sup>26</sup> In the LAASR study, while progression-free survival in patients with RN was 91% at last follow-up extending out to 6 months,<sup>26</sup> not all RN lesions were successfully treated with LITT. Factors contributing to local failure have not been studied. Here we describe the course of two patients treated with immunotherapy and stereotactic radiosurgery (SRS) to brain metastases who were then treated with LITT for RN. In both cases LITT was insufficient to control patient symptoms and both required subsequent craniotomy for resection of the LITT-treated lesion. Histological analysis of post-LITT tissue is presented with the hope of contributing to the better understanding of the post-LITT immunological milieu in the patient with RN.

## Illustrative Cases

### Case 1

#### Clinical Presentation

A 64-year-old male presented with a 30 pack-year smoking history, atrial fibrillation on aspirin, and a family history of lung cancer. He was initially evaluated for productive cough, shortness of breath, and chest pain and was found to have a right 6.7 × 5.6 cm hilar mass, mediastinal and hilar lymphadenopathy, pleural and pericardiac effusions, and multiple liver and spleen lesions (T4N3M1). Histological evaluation of lung lesion revealed poorly differentiated adenocarcinoma with PD-L1 highly expressed in 90%–100% of tumor cells. No targetable mutations were identified and DNA variant detected/allelic fractions showed 50% of KRAS c.35G > A (p.Gly12Asp) mutation, with 8% cells carrying KRAS c.404G > C (p.Arg135Thr) mutation. Magnetic resonance imaging (MRI) showed six brain metastases, the largest of which was a 2.5 × 2.0 × 1.6 cm hemorrhagic lesion located in the left parieto-occipital periventricular region (Fig. 1A). Given that the patient was neurologically asymptomatic, he elected to defer surgery to the largest lesion and was treated with single-fraction stereotactic radiosurgery (SRS) and all six lesions were prescribed 18 Gy to the 50%–70% isodose surface. The parieto-occipital lesion specifically was treated with 18 Gy to the 50% isodose surface. The patient was then treated with four cycles of PD-1 inhibitor pembrolizumab with significant improvement in lung lesion size.

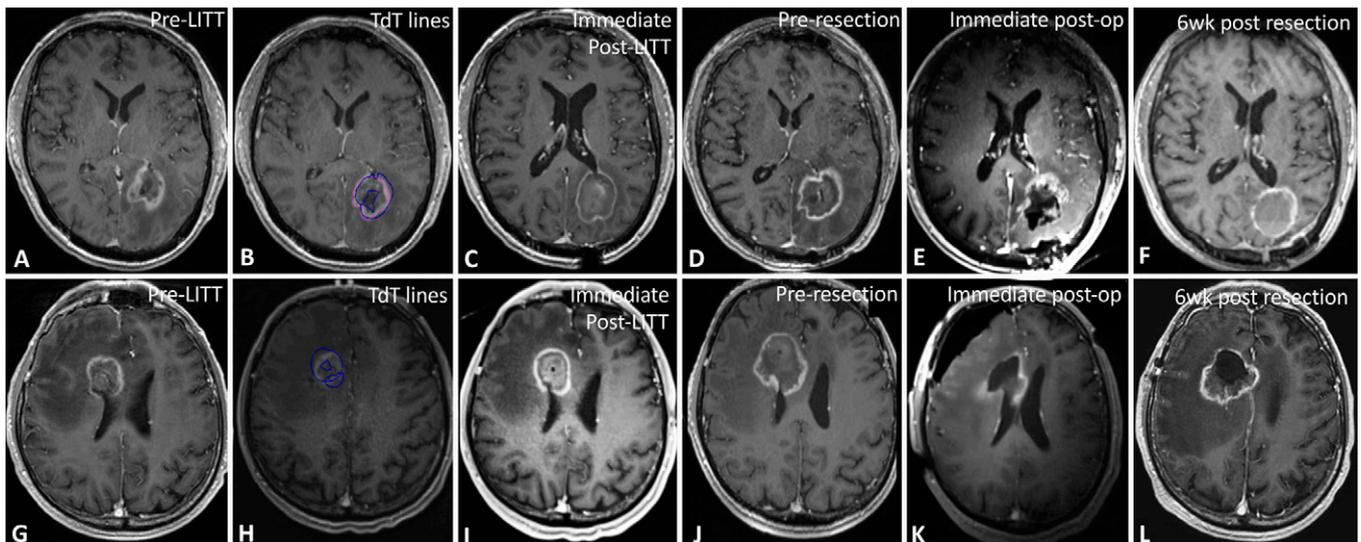
The left parieto-occipital lesion remained stable in size at 6-week follow-up MRI.

Three months after SRS, the patient presented to the emergency department with confusion, gait instability, and right-sided hemiparesis. Repeat MRI showed further growth of the parieto-occipital lesion to 3.5 × 2.5 cm with worsening surrounding fluid-attenuated inversion recovery signal. Symptoms improved with steroids and patient was offered but declined craniotomy. Repeat imaging 1 month later showed further increase in lesion size (3.5 × 3.0 cm) and edema; magnetic resonance perfusion images were suggestive of RN. Immunotherapy was held due to the patient requiring steroids for symptoms management. Treatment options of Avastin (Genentech Inc), craniotomy, or LITT were discussed at this time and patient elected to undergo LITT. LITT was performed using the NeuroBlate (Monteris Medical) system and it was believed that complete ablation was achieved (Fig. 1B and C). Biopsy at the time of LITT showed no evidence of tumor. Initial post-LITT MRI showed the expected well-demarcated rim-enhancing lesion corresponding to the LITT cavity associated with improvement in the surrounding edema. Unfortunately, despite improvement in imaging, the patient was still unable to be weaned from steroids and follow-up MRI of the brain at 3 months post-LITT again showed further growth of the LITT-treated lesion (4.7 × 3.5 cm) (Fig. 1D).

The patient therefore agreed to undergo craniotomy. Intraoperatively, a firm rubbery capsule was noted around the entire lesion. Perilesional white matter was soft and edematous, without additional vascular proliferation and otherwise appeared relatively normal. The anterior aspect of the capsule was noted to be tightly adherent to the left lateral ventricular wall and was left in situ as residual. The remainder of the encapsulated lesion was removed. At 3-month follow-up after craniotomy, the patient was no longer taking steroids with complete resolution of his confusion and hemiparesis and was able to be restarted on immunotherapy. Currently, the patient has stable remaining disease in the chest only and remains on immunotherapy 16 months postcraniotomy.

#### Histological Analysis

Grossly, the resected lesion had a clearly defined firm rubbery thick white capsule that was easily demarcated from the surrounding soft white matter. On transection of the lesion the central portion was noted



**FIG. 1.** MRI with gadolinium in case 1 (A–F) and case 2 (G–L). The lesion pre-LITT (A and G), thermal damage threshold (TdT) lines at completion of LITT (B and H), immediate post-LITT (C and I), pre-resection (D and J), immediately postresection (E and K), and 2 months postresection (F and L).

to be soft, white, and friable, with histological evidence of extensive coagulative necrosis devoid of viable cells. Histology of the capsule showed dense granulation tissue with small vessel neovascularization, abundant reticulin fibers, and numerous lymphocytes, microglia, and macrophages (Fig. 2). Reactive astrogliosis was noted in the surrounding brain parenchyma. Immunohistochemical staining for pan-cytokeratin did not detect viable tumor cells, and Ki-67 was present in a few inflammatory cells. The prominent immune cell infiltrate within the capsule was composed of predominantly chronic inflammatory cells, including CD163/CD68<sup>+</sup> macrophages, few cytotoxic CD8<sup>+</sup> T lymphocytes and CD20<sup>+</sup> B lymphocytes. Clusters of CD138<sup>+</sup> plasma cells were also identified at a distance to the necrotic center, particularly in perivascular niches. Staining for PD-1/PD-L1 was negative.

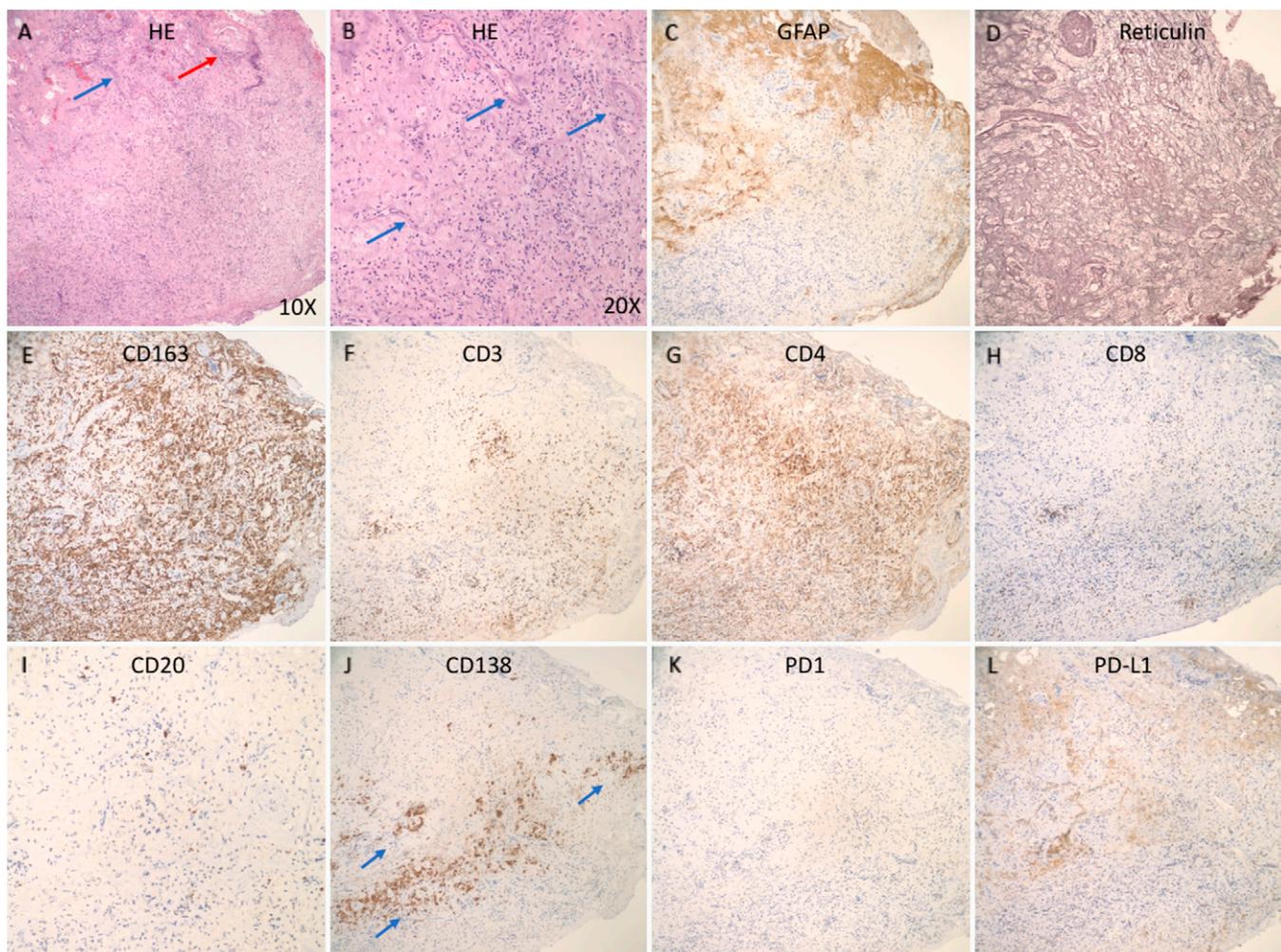
## Case 2

### Clinical Presentation

A 79-year-old male presented with seizures, extensive cardiovascular disease taking aspirin and Brilinta (AstraZeneca), and

family history of bladder cancer. He was initially evaluated for worsening back pain, and workup revealed metastatic lesions in right clavicle, manubrium, right scapula, L1 and L4 vertebral bodies, cystic right lower lobe lesion, right hilum and liver lesions. Biopsy revealed malignant melanoma with extensive necrosis and spindled epithelioid cells. Immunostaining was strongly positive for S100, MelanA, and HMB45. Genetic tumor testing revealed an NRAS mutation only. MRI revealed five brain metastases; the largest was 2.8 × 2.5 cm with internal hemorrhage located in the right anterior basal ganglia extending superiorly into the periventricular white matter (Fig. 1G). The patient underwent single-fraction radiosurgery, where 18 Gy to the 50%–70% isodose surface was prescribed to all five lesions. Specifically, 18 Gy to the 50% isodose surface was prescribed to the periventricular lesion. The patient was then treated systemically with combination ipilimumab/nivolumab.

Four months after SRS, the patient presented to the emergency department with confusion and incontinence concerning for seizures. He was prescribed levetiracetam and dexamethasone. MRI of



**FIG. 2.** Case 1. **A and B:** Hematoxylin and eosin-stained sections at low and high magnifications, respectively. Granulation tissue with prominent capillary and small vessel proliferation (*blue arrows*), macrophages and mixed neutrophilic and lymphoplasmacytic inflammation. Vessel with fibrin thrombi shown with *red arrow*. **C:** Reactive astrogliosis in the brain parenchyma adjacent to the “pseudocapsule” is highlighted with GFAP immunostaining. **D:** Abundant reticulin fibers within the granulation tissue (“pseudocapsule”) are depicted with reticulin stain. **E:** CD163 immunostaining shows marked diffuse infiltration of microglial cells and macrophages in granulation tissue and adjacent brain parenchyma. **F:** Small CD3<sup>+</sup> T lymphocytes infiltrated granulation tissue. **G:** CD4<sup>+</sup> immune cells. **H:** A smaller subset of CD8<sup>+</sup> lymphocytes present. **I:** Scattered B lymphocytes are highlighted with CD20 immunostaining. **J:** Aggregates of CD138<sup>+</sup> plasma cells are noted focally (*blue arrows*). **K and L:** Rare cells are highlighted with PD1 and PD-L1 antibodies.

the brain showed slight growth of the right frontal lesion (3 × 2.6 cm) associated with significant increase in perilesional edema. The option of craniotomy was discussed, but given the patient's older age, patient and family were reluctant to proceed. The alternatives of Avastin and LITT were therefore discussed, and the patient chose to undergo LITT given concerns about the possible systemic side effects of Avastin. Laser ablation was performed using the NeuroBlate system, and almost complete ablation was achieved except where enhancement extended into the corpus callosum (Fig. 1H and I). Biopsy at the time of LITT showed no evidence of tumor (Fig. 3A–C). Post-LITT MRI over the subsequent 3 months showed continued increase in lesion size to 4 × 3.6 cm and increase in surrounding edema with extension of enhancement further into the corpus callosum. The patient progressed clinically and developed left hemiparesis 3 months after LITT, at which time he agreed to right frontal craniotomy.

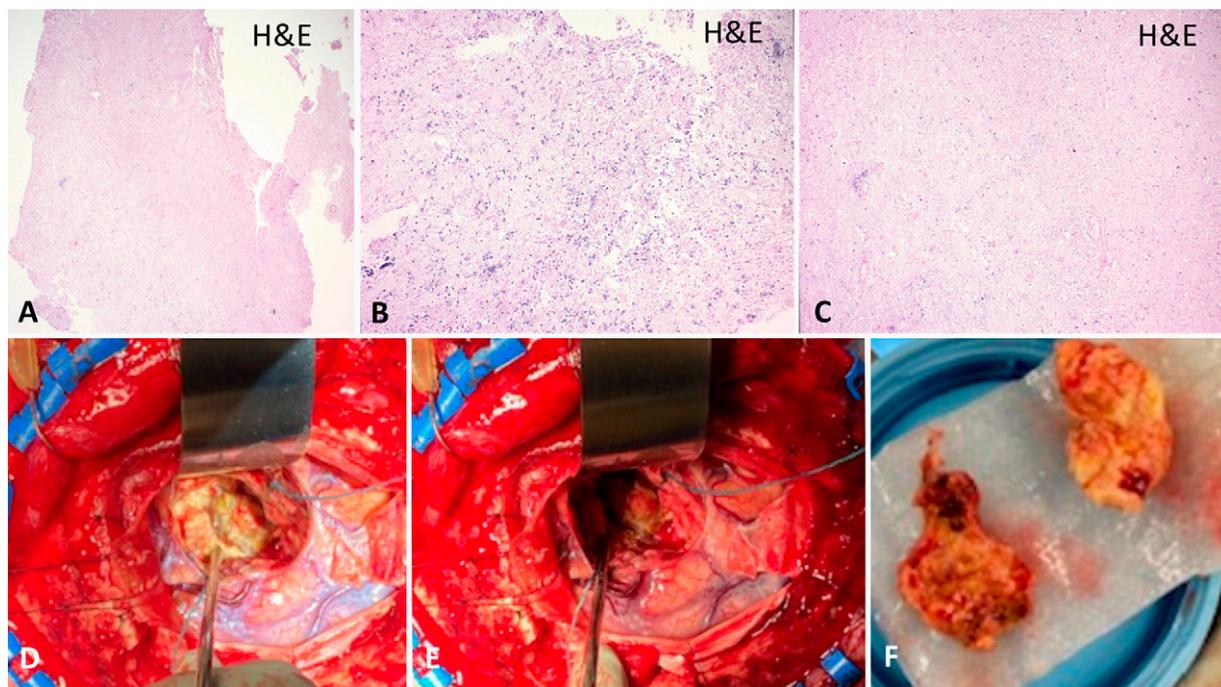
Intraoperatively, firm rubbery tissue was again identified (Fig. 3D–F). The demarcation between the lesion and the surrounding brain, however, was not clearly identifiable in this case and significant vascular proliferation was seen grossly outside the capsule. At the inferolateral border of the firm tissue, a dark discolored independently recognizable nodule was identified. Perilesional white matter was noted to be firmer than normal and was debulked laterally and anteriorly. Periventricular and posterior margins were not explored to avoid neurological injury. The patient's hemiparesis improved postoperatively but recurred 2 months later, and MRI at this time showed further lesional growth for which he was prescribed Avastin. At last follow-up 6 months after starting Avastin, the patient has also been restarted on immunotherapy with stable systemic disease.

### Histological Analysis

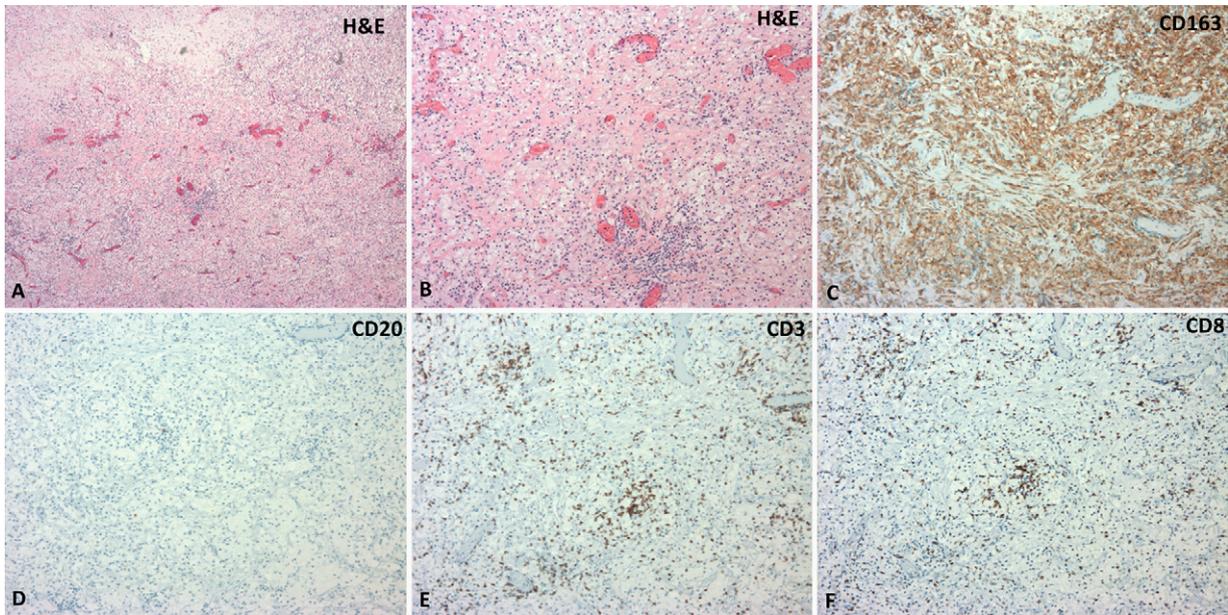
Grossly, the resected lesion was divided into three separate specimens: a firm tissue capsule surrounding a friable white center, a distinctly discolored nodule separate from the fibrous capsule, and surrounding firm white matter. Histological analysis of the friable center tissue showed only evidence of coagulation necrosis devoid of viable cells (Fig. 4). None of the specimens contained viable tumor. The discolored nodule showed residual melanin pigment mainly within macrophages and in the form of extracellular debris. The capsule and adjacent firm white matter were histologically similar and showed significant demyelination, reactive astrocytosis, vascular hyalinization and chronic inflammatory cells also with abundant reticulin staining. An abundance of CD68<sup>+</sup> macrophages was again noted along with smaller foci of predominantly perivascular T lymphocytes. Only very few intermixed B lymphocytes were present. There was no significant difference in the distribution of the CD3 versus CD8 antigens, suggesting that most T cells were suppressor T lymphocytes (Fig. 4).

### Discussion

As far as the authors are aware, the histological composition of metastatic post-LITT lesions for RN has not been previously described. Likewise, there is no published correlation of gross pathology specimens and radiological imaging of these lesions particularly in post-SRS lesions treated with LITT. Elder et al.<sup>27</sup> described histological findings of post-LITT glioblastoma tissue in a patient who had undergone LITT a few days prior to surgical resection. Histological changes showed a central region of necrosis surrounded by a rim of granulation



**FIG. 3.** Case 2. Histological analysis (A–C) of tissue obtained by biopsy prior to LITT, showing fragments of necrotic tissue with scattered hyalinized blood vessels, macrophages, and focal reactive changes. Original melanoma nodule pre- (D) and postresection (E) within the surgical cavity. Surgical specimen (F): lesion capsule (*left*), RN lesion (*right*).



**FIG. 4.** Case 2. **A and B:** Hematoxylin and eosin-stained sections at low and high magnifications, respectively. Note multiple vessels with fibrin thrombi and numerous small vessels present in granulation tissue. **C:** CD163 immunostaining showing marked diffuse infiltration of microglial cells and macrophages. **D:** Scattered B lymphocytes are highlighted with CD20 immunostaining. **E:** CD3<sup>+</sup> T lymphocytes diffusely infiltrate granulation tissue. **F:** Similar subset of CD8<sup>+</sup> lymphocytes is present.

tissue containing CD68<sup>+</sup> macrophages, with viable tumor cells adjacent to these.

### Observations

In this case report, the histopathological features of two post-LITT lesions are described. While there were many similarities between the two cases, the primary tumor pathology, immunotherapy treatment, and eventual outcomes were significantly different. In both cases LITT volume was large with post-LITT cavity diameters of 3 cm. It is possible that if LITT were considered earlier, perhaps ablation would have been more successful. In the first case, single agent immunotherapy and SRS was used for treatment in a patient with a known PD-1+ lung cancer. In the second case, combined immunotherapy agents were used in conjunction with SRS for treatment of melanoma. It has been shown that checkpoint inhibitor immunotherapy can exacerbate postradiation inflammation, but it has not been well studied if dual immunotherapy may predispose the patient to a more robust inflammatory response as was seen in the patient in case 2. Both lesions were of the same size at the time of LITT and post-LITT imaging appeared quite similar. The time between LITT and subsequent surgical resection in both of our patients was approximately 3 months. In the first case, underlying RN was controlled by LITT and surgical resection of the post-LITT lesion resulted in resolution of intracranial progression. Interestingly, LITT resulted in the creation of a clean fibrous capsule that actually facilitated resection of the lesion with good clinical result. As expected, histologically the center of the post-LITT lesion contained coagulative necrosis. The capsule showed evidence of granulation tissue and adjacent brain showed only mainly reactive astrogliosis. In the second case, RN progressed despite LITT. Histologically, while firm tissue surrounding central necrosis was also seen intraoperatively, there was no cleanly defined capsule. In addition, in comparison to the soft edematous white matter surrounding

the lesion in the first case, the white matter in this second case was firm with extensive macrophage and some T-cell infiltrate, changes consistent with ongoing RN. This suggests perhaps that in the patient in case 1, the area of RN was adequately covered by the LITT ablation whereas in the patient in case 2, even though the enhancing lesion appeared fully ablated, the region of RN was not. This may explain why not all RN lesions respond to LITT and suggests that a better radiological understanding of what defines the edge of a RN lesion is needed. Alternatively, the patient in case 1 received Avastin therapy prior to LITT, whereas the patient in case 2 never received Avastin and this difference could also be postulated to explain perilesional changes around the LITT lesion.

The immune cell composition of brain metastases is being increasingly studied and has been shown to contain a high number of lymphocyte subtypes of which can be influenced by local microenvironment and type of malignancy.<sup>28-32</sup> Immune regulatory molecules driving myeloid and lymphocytic cells (CD40L, IL6R, INHBA, AREG) are highly expressed, with specific increase in autoimmune inflammation mediators and specific enrichment of IL6 in microglia and TREM1 in microglia/macrophages.<sup>28</sup> RN histology also demonstrates marked inflammatory changes with abundant infiltration by CD3<sup>+</sup> T cells and CD68<sup>+</sup> macrophages but drivers of this process have been less well studied.<sup>29,30</sup> It remains unclear if the CD68<sup>+</sup> macrophages represent residual surviving tumor associated macrophages, which themselves can arise from resident microglia or peripheral monocytes, or if they are recruited as a part of the reactive inflammatory process in response to radiation. The presence of the same inflammatory cells in the capsule of a LITT lesion however raises the question of whether these cells may be part of a standard response to white matter injury regardless of initiating mechanism or whether they are the cause of the self-perpetuating process.

The number of patients undergoing combined SRS and immunotherapy with subsequent development of RN is likely to continue to

increase.<sup>31</sup> It is therefore increasingly important to better understand the pathophysiology of RN and how treatment can be used more effectively. An upcoming trial at the University of Florida (NCT04187872) will investigate the immune effects of LITT and pembrolizumab in adult patients with brain metastases from melanoma, NSCLC, or renal cell carcinoma recurring post-SRS, primary cancers approved for treatment with immune-checkpoint inhibitors by the Food and Drug Administration (<https://clinicaltrials.gov>). Characterization of immune cell response in LITT integrated with immunotherapy will hopefully provide a better understanding of underlying mechanisms of the efficacy or failure of combination SRS and immunotherapy as well as LITT in this patient population. Limitations of this study include the small number of patients and significant clinical differences between the two clinical scenarios, making comparison as well as drawing conclusions difficult. In addition, complex analysis of pre-LITT tissue was not available to be compared to postresection tissue. Moreover, while providing a valuable snapshot of the biology of LITT-treated RN, further studies are necessary to delineate the roles of individual cell types in this process as well as the identification of possible inflammatory biomarkers that could help understand the pathophysiology behind these complex inflammatory complications.

### Lessons

Criteria for selecting the best RN patients for LITT therapy remains unclear. Given two similarly sized lesions and not too dissimilar clinical histories but with differing outcomes, further investigation is clearly needed to identify predictors of response to LITT in the setting of SRS and immunotherapy-induced RN.

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### Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

### Author Contributions

Conception and design: Fomchenko, Chiang. Acquisition of data: Fomchenko, Leelatian, Darbinyan, Huttner. Analysis and interpretation of data: Fomchenko, Leelatian, Darbinyan, Huttner. Drafting the article: Fomchenko, Huttner, Chiang. Critically revising the article: Fomchenko, Darbinyan, Huttner, Chiang. Reviewed submitted version of manuscript: Fomchenko, Darbinyan, Huttner, Chiang. Approved the final version of the manuscript on behalf of all authors: Fomchenko.

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