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Tumor location as a risk factor for severe immune-related adverse events

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ABSTRACT

Immune-related adverse events (irAEs) can cause severe morbidity and mortality, and they impair treatment with immune checkpoint inhibitors (ICI). Risk factors for irAEs are not well understood.

We observed cases of patients having tumor deposits in their liver and lung during a workup of irAEs, which led us to hypothesize that the presence of tumor in an organ would increase the odds of developing severe irAEs in that organ. We then performed a retrospective cohort study that included patients who received an ICI for the treatment of cancer and were hospitalized between February 2011 and November 2021 at the Massachusetts General Hospital. We reviewed 384 patients hospitalized with concern for any irAE. A clinical diagnosis of ICI-related hepatitis occurred in 18% of patients with liver tumor deposits versus 8% of those without (OR 2.23, 95% CI (1.10 to 4.43), p=0.02). ICI-related pneumonitis occurred in 10% of patients with lung tumor deposits versus 4.4% of those without (OR 2.45, 95% CI (1.06 to 6.36), p=0.047). A combined analysis for liver and lung lesions demonstrated that the presence of tumor deposits in an organ increased the odds of having an irAE in that organ by over twofold (OR 2.31, 95% CI (1.34 to 3.99), p=0.002).

Our results suggest that the presence of tumor deposits may represent a novel risk factor for severe irAEs in that organ.

BACKGROUND

Immune checkpoint inhibitors (ICIs) can effectively treat patients with cancer across many clinical settings.[1] However, ICIs can cause side effects in almost any organ system,[2–4] which are broadly classified as immune-related adverse events (irAEs). Proposed mechanisms of irAEs[3] include T-cell responses to commensal or tumor-unrelated autoantigens,[5–7] recognition of autoantigens shared between tumors and healthy tissues,[8 9] autoantibody production,[10] inflammatory cytokine stimulation,[11 12] and direct binding to ICI targets expressed in healthy tissues.[13] irAE risk factors include prior autoimmune disease,[14 15] previous history of an irAE,[16] combination therapies, and longer ICI exposure.[4] Some primary tumors have been associated with specific irAEs in their organs of origin; for example, lung cancer is associated with an increased risk of ICI-related pneumonitis (irPneumonitis), and melanoma is associated with an increased risk of developing vitiligo.[17] Cases of tumor metastases colocalizing with organ inflammation in biopsies of irAEs affecting the stomach[18] and heart[7] have been reported. This raised the question of the influence of tumor presence on ICI-provoked inflammation.

We hypothesized that tumor deposits in an organ increase the risk for the development of a clinically significant irAE in that organ. We first observed two clinical cases that inspired this hypothesis: one case of ICI-related hepatitis (irHepatitis) with microscopic tumor foci present in a non-focal biopsy and a case of irPneumonitis in a patient with radiographically evident lung metastases. We next examined a retrospective cohort and discovered that radiographic evidence of tumor in the liver or lungs was associated with an increased risk of irAEs in the tumor-infiltrated organ. These results suggested that the presence of tumor deposits in an organ may lead to inflammation that presents clinically as an irAE.

METHODS

Study design and participants

Patients were admitted to the Massachusetts General Hospital (MGH) from February 2011 to November 2021, were over 18 years of age, and had received an ICI for cancer treatment (Severe Immunotherapy Complications Service database).[19] Pathology reports were collected via Mass General Brigham Research Patient Data Repository (RPDR). Radiology reports from one CT report preceding and one CT report proceeding the

irAE hospitalization were collected via RPDR, compiled using MATLAB text analysis (R2022a, Mathworks), and manually reviewed for the presence of tumors in the lung and liver. Patients were classified by internists and medical oncologists as having irHepatitis or irPneumonitis based on documentation by treating clinicians, laboratory findings, radiology reports, pathology results, and the initiation of steroid therapy. irHepatitis was defined as a diagnosis of exclusion for transaminitis after thrombus, infection, co-offending medications, concomitant ICI-related myocarditis, and biliary etiologies were ruled out, and/or if transaminitis improved with corticosteroid administration. A majority of cases were further confirmed with a liver biopsy. irPneumonitis was defined as a diagnosis of exclusion for hypoxemia with radiographic infiltrates after pulmonary embolism, infection, chronic obstructive pulmonary disease, and congestive heart failure were ruled out and/or hypoxemia improved with corticosteroid administration. All cases were reviewed by two clinicians, and in the case of discordance, the case was discussed with a third clinician to minimize interobserver variability and ensure diagnostic consistency; in these cases, a full review of the patient history and radiographic imaging was performed by all parties. Patients with potential co-offending medications (eg, transaminase elevation from high doses of acetaminophen) were classified as not having an irAE. Patients who received local radiation to the lung were excluded from irPneumonitis analyses. The primary analysis assessed the impact of tumor in an organ as a risk factor for an irAE in that organ. Supporting analyses are reported as well in the online supplemental tables.

Statistical analysis

356 patients were estimated to give 80% power to detect a 100% increase in the odds of irHepatitis assuming a 10% population incidence and a 50% increase in the odds of irPneumonitis assuming a 5% population incidence (G*Power, V.3.1.9.6). All analyses were performed using R Statistical Software (V.4.1.2; R Core Team 2021) with packages *readxl, rmeta, easystats, dplyr, gtsummary, magrittr, glue, ggbeeswarm, ggfortify, survival, epitools,* and *metafor.* Multivariable binomial logistic regression was used to determine ORs (*irAE~TumorDeposits +Age + Sex + Race*). Liver and lung metastases were calculated to occur independently in each patient ($p_{livertumors} * p_{lungtumors} \approx p_{bothtumors} \approx 14\%$), so liver-specific and lung-specific analyses were run independently in the same cohort of patients using the presence of tumor and irAE for each organ. These results were combined, and a random-effects meta-analysis was used to estimate the overall effect size of tumor presence on irAE risk.

RESULTS

Cases

Case 1: A patient in their 70s with uveal melanoma with metastases to bone and liver initiated ICI therapy with ipilimumab (3 mg/kg) and nivolumab (1 mg/kg). After cycle 2, the patient developed a biopsy-proven skin hypersensitivity reaction and was found to have Grade 1 transaminitis without bilirubinemia.[20] The transaminitis resolved after receiving methylprednisolone 1.5 mg/kg intravenous for 3 days. When steroids were transitioned to oral prednisone, the patient developed Grade 2 transaminitis. A non-targeted liver biopsy showed inflammation around metastatic melanoma occupying about 2 mm of the liver biopsy (figure 1A). Liver enzymes normalized with continued oral prednisone. 2 months later, the patient was tapered to prednisone 15 mg daily and developed Grade 3 transaminitis. A repeat liver biopsy was consistent with irHepatitis; no metastatic lesions were observed (figure 1B). The patient was initiated on mycophenolate mofetil and high-dose steroids. The liver metastases progressed, and the patient died 7 months later.

Case 2: A patient in their 80s with a history of immune thrombocytopenia (ITP) and BRAF wild-type cutaneous melanoma with pulmonary metastases was treated with nivolumab 240 mg intravenous every 2 weeks (figure 1C). After six cycles, CT imaging of the chest showed responses in the pulmonary metastases but new bilateral consolidations concerning for irPneumonitis. 6 weeks later, the patient was found to desaturate with ambulation to 85–87% on room air, and a repeat chest CT showed continued improvement in the patient's lung masses with progressive infiltrates suggestive of Grade 3 irPneumonitis (figure 1D). Prednisone 125 mg daily was initiated with improvement in oxygenation, and the patient was tapered off of steroids in 6 weeks. 9 months later, the patient developed radiographic signs of progressive disease and was re-initiated on nivolumab, which led to a flare in the patient's ITP and hemolytic anemia requiring steroids. irPneumonitis did not recur nor did the melanoma respond to therapy, and the patient died 9 months after resuming nivolumab.

Population demographics

We aimed to investigate the correlation between the presence of radiographic evidence of tumors in the liver or lungs and a diagnosis of irAEs in these organs. These sites are routinely imaged and common anatomical locations for both irAEs and radiographically evident cancer involvement. Of 850 patients admitted to MGH with concern for an irAE, 384 patients had confirmed irAEs (figure 2). The patients were 58% men, 94% Caucasian, and their mean age was 68 years old (table 1). Melanoma was the most common malignancy (48%), followed by thoracic (19%), gastrointestinal (10%), genitourinary (8%), gynecologic (5%), and other (11%) tumors. Programmed cell death protein-1 (PD-1) inhibition (pembrolizumab, nivolumab) was the most common ICI therapy (53%), followed by combination PD-1/cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibition (ipilimumab/nivolumab; 24%), CTLA-4 inhibition (ipilimumab; 15%), and others (9%).

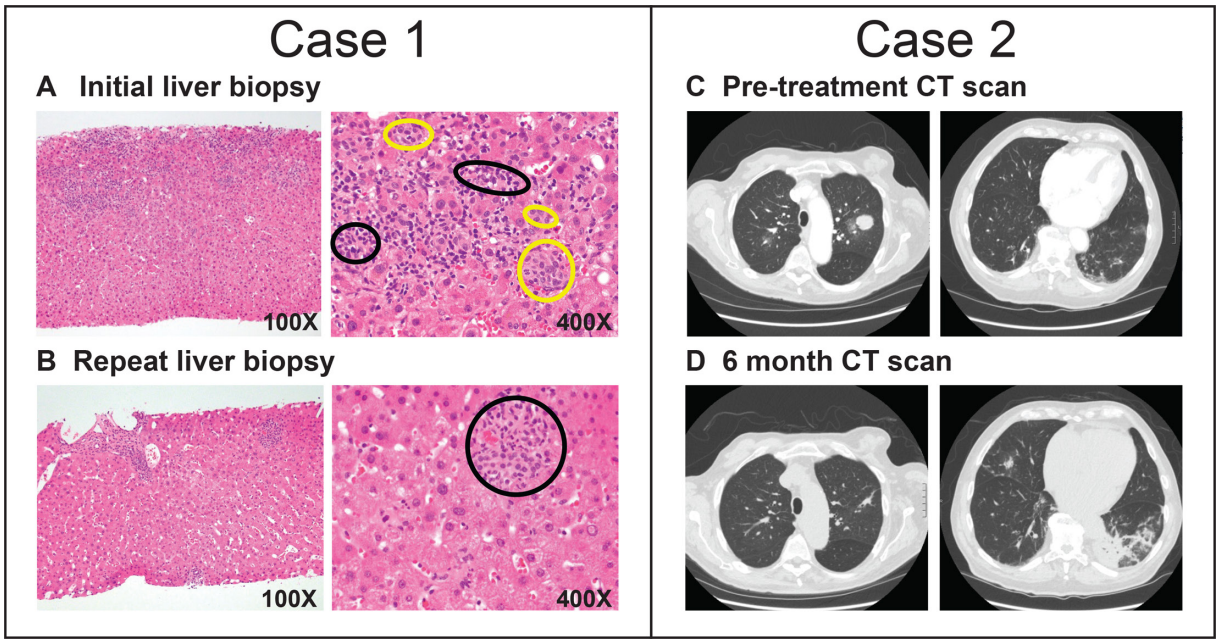

Figure 1 Clinical cases of tumor infiltration in the organs affected with immune-related adverse events. (A, B) Pathologic correlates of Case 1. In (A) H&E of a liver biopsy from Case 1 at (left) 100x magnification and (right) 400x magnification shows infiltration of liver parenchyma with uveal melanoma and lymphocytes. In (B) a repeat biopsy from Case 1 collected 2 months later shows findings consistent with ICI-related hepatitis and no metastases at (left) 100x and (right) 400x magnification. Areas enriched with clusters of cancer cells with large nuclei and nucleoli (yellow circles) and lymphocytes (black circles) are highlighted to demonstrate examples of cell populations that are interspersed in the tissue. (C, D) Radiographic correlates of Case 2. In (C) contrast-enhanced CT imaging shows areas of (left) metastatic melanoma and (right) lung parenchyma prior to ICI initiation. In (D) non-contrast CT imaging 6 months after ICI treatment initiation shows the same regions as in (C) to highlight evidence of (left) antitumor response and (right) ICI-related pneumonitis, respectively. ICI, immune checkpoint inhibitor.

Tumor deposits increase the risk of irHepatitis and irPneumonitis

Among 384 patients, 88 (23%) had liver tumor deposits by CT imaging and 42 (11%) were diagnosed with irHepatitis. A clinical diagnosis of irHepatitis occurred in 18% of patients with liver tumor deposits versus 8.8% of those without (OR 2.23, 95% CI (1.10 to 4.43), p=0.02; figure 3A, online supplemental tables 1,2). In strictly biopsy-proven irHepatitis (34 of 42 cases, 81%), the presence of tumor deposits in the liver remained significantly associated with irHepatitis (OR 2.54, 95% CI (1.18 to 5.33), p=0.01; online supplemental table 3).

Among the 376 patients evaluable for irPneumonitis, 219 (58%) had lung tumor deposits by CT imaging, and 30 (8%) were diagnosed with irPneumonitis. irPneumonitis occurred in 10% of patients with lung tumor deposits versus 4.4% of those without (OR 2.45, 95% CI (1.06 to 6.36), p=0.047; figure 3B, online supplemental tables 4,5).

We adjusted for various possible confounders. The association between the location of the tumor and irAE in the same tissue remained significant after controlling for demographics (age, sex, and ethnicity; online supplemental table 5). There were no significant differences in the duration of ICI exposure for patients with and without irAEs and with and without tumor deposits in liver or lung. An exploratory analysis found that evaluable patients with primary lung or pleural cancers (non-small cell lung cancer, small cell lung cancer, or mesothelioma; n=65) had an increased risk for the development of irPneumonitis (online supplemental table 6), as has been reported in the literature.[17] We are underpowered to assess the impact of primary liver cancers (hepatocellular or biliary malignancies; n=12) on irHepatitis risk.

A combined analysis for liver and lung demonstrated that the presence of either primary or metastatic tumor deposits in an organ increased the odds of having an irAE in that organ by over twofold (OR 2.33, 95% CI (1.35 to 4.02), p=0.002; figure 3C). Lung tumors did not increase the likelihood of irHepatitis (online supplemental table 7), and liver tumors did not increase the likelihood of irPneumonitis (online supplemental table 8), suggesting that tumor deposits in an organ did not associate with increased risk of irAE in distant organs. We then assessed the risk of metastatic disease as a risk factor for irAEs in the location of metastases (online supplemental figure 1; online supplemental tables 9,10). Liver metastases were associated with irHepatitis (OR=2.24, 95% CI (1.06, 4.57), p=0.029). Lung metastases trended towards an increased frequency of irPneumonitis (OR=2.07, 95% CI (0.81, 5.73), p=0.141). A meta-analysis of both metastatic sites suggests that metastatic lesions in an organ are associated with an irAE in that organ (OR=2.17, 95% CI (1.22 to 3.99), p=0.009). These results suggest that the presence of tumors in an organ is associated with an increased risk of an irAE in that organ.

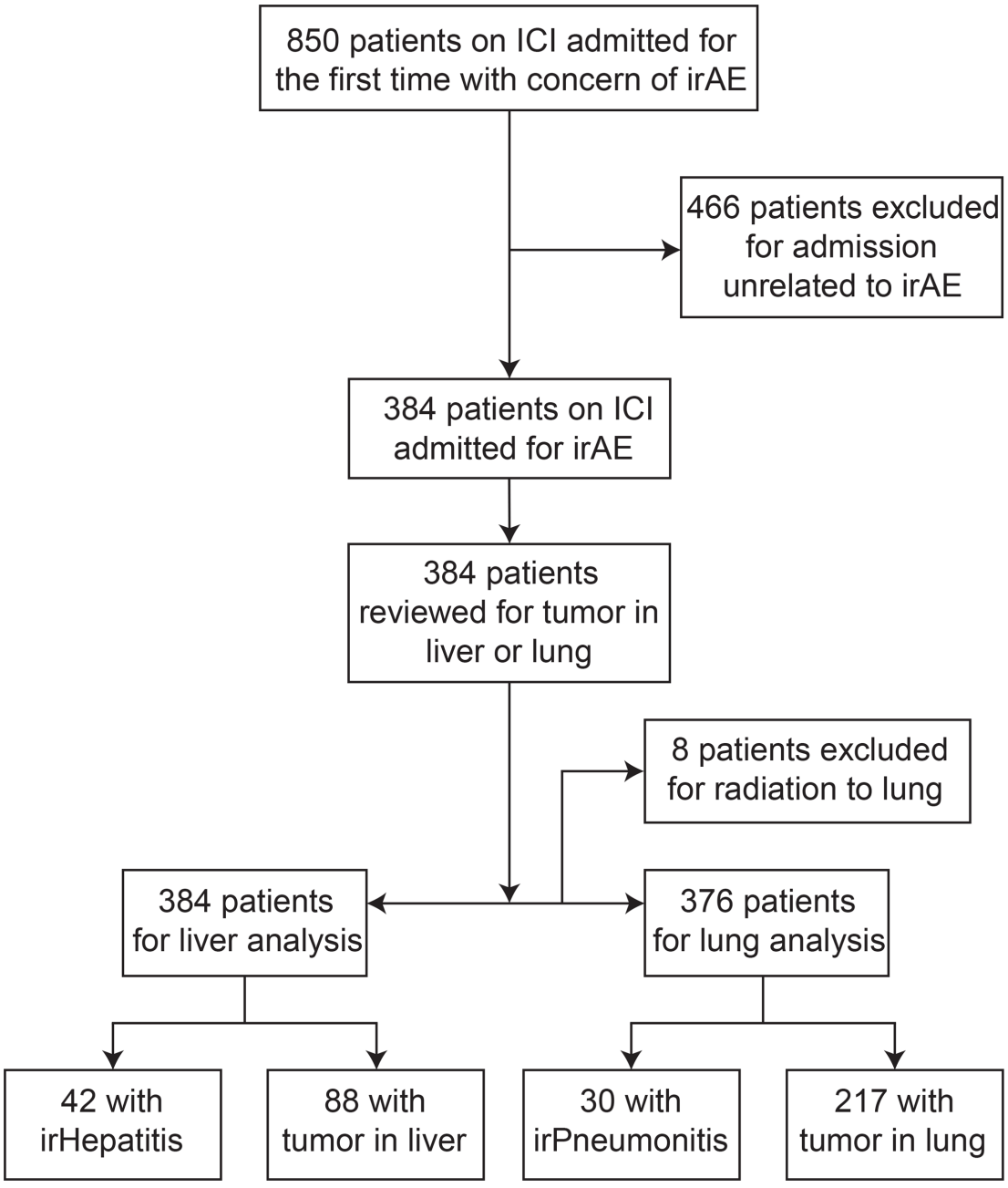

Figure 2 Patient inclusion and exclusion analyses. A flow diagram showing the number of patients excluded from the study for meeting the listed clinical criteria as well as those with the irAEs and tumor deposits in the organs of interest. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; irHepatitis, ICI-related hepatitis; irPneumonitis, ICI-related pneumonitis.

DISCUSSION

Here we report two observational cases of tumor deposits in the liver and lungs of patients with severe irAEs and a retrospective cohort study of 384 patients demonstrating an association between tumor deposits and severe irAEs. This finding implicates the role of tumor infiltration in the development of inflammation that leads to irAE diagnoses in some patients. We hypothesize that the inflammation associated with tumor deposits can either (1) trigger local tissue damage and an irAE that can resolve after the tumors are cleared or (2) lead to a true break in immune tolerance that will persist. Exploring and distinguishing these mechanisms may help us to better manage the subset of patients for whom tumor infiltration plays a role in the development of irAEs.

Our study investigated patients hospitalized with suspected irAEs and deeply characterized severe irAE phenotypes in the liver and lung. Although we were able to validate suspected irHepatitis cases with liver biopsies, many suspected irPneumonitis cases could not be proven histologically because of the risk associated with lung biopsies. We leveraged multidisciplinary diagnostic expertize at our institution to minimize this limitation[21] and performed deep clinical phenotyping. Our study was

Table 1 Population demographics (n=384)

	Entire cohort	irHepatitis	irPneumonitis
Age (average, (range))	68 (22–98)	66 (32–85)	71 (46–89)
Sex			
Male	222 (58%)	26 (63%)	14 (47%)
Female	162 (42%)	16 (37%)	16 (53%)
Race			
White	363 (94%)	37 (88%)	28 (93%)
Asian	10 (3%)	2 (5%)	0 (0%)
Black	5 (1%)	2 (5%)	1 (3%)
Unknown	6 (2%)	1 (2%)	1 (3%)
Primary tumor			
Melanoma	183 (48%)	21 (50%)	12 (40%)
Thoracic	71 (19%)	8 (19%)	10 (33%)
Gastrointestinal	39 (10%)	5 (12%)	1 (3%)
Genitourinary	30 (8%)	3 (7%)	2 (7%)
Gynecologic	19 (5%)	1 (2%)	1 (3%)
Head/neck	15 (4%)	0 (0%)	0 (0%)
Neurological	9 (2%)	3 (7%)	0 (0%)
Breast	7 (2%)	1 (3%)	2 (7%)
Hematological	5 (1%)	0 (0%)	1 (3%)
Skin	5 (1%)	0 (0%)	1 (3%)
Sarcoma	1 (0%)	0 (0%)	0 (0%)
ICI			
Pembrolizumab	140 (36%)	11 (26%)	11 (37%)
Ipilimumab+nivolumab	92 (24%)	20 (48%)	8 (27%)
Nivolumab	62 (16%)	6 (14%)	7 (23%)
Ipilimumab	56 (15%)	1 (2%)	0 (0%)
Atezolizumab	16 (4%)	3 (7%)	2 (7%)
Durvalumab	9 (2%)	1 (2%)	1 (3%)
Cemiplimab	6 (2%)	0 (0%)	1 (3%)
Other	3 (1%)	0 (0%)	0 (0%)

ICI, immune checkpoint inhibitor; irHepatitis, ICI-related hepatitis; irPneumonitis, ICI-related pneumonitis.

conducted within a single, academic, tertiary care center; included patients that were predominantly white; and was retrospective in nature. These factors may introduce potential population bias and limit the generalizability of our findings to more diverse populations.

The relationship between tumor deposits and irAEs may be affected by different tumor histologies, less severe irAEs, irAEs impacting organs outside of the lung and liver, and tumor burden. The inability of conventional CT imaging to detect small metastatic deposits likely underestimates the true incidence of metastases in the lung and liver. Furthermore, CT imaging has limited sensitivity to detect metastases in other organs such as the stomach or heart, where metastatic lesions are commonly detected in autopsies.[22 23] ICI-related gastritis with co-occurring microscopic deposits of melanoma has been described,[18] and cases of ICI-related myocarditis have been reported where metastases were only identified at the time of autopsy.[7] Interestingly, a recent series of 110 patients with large, radiographically evident cardiac metastases prior to ICI treatment reported a higher rate of cardiac ICI-related adverse events[24] than expected.[25] The detection of small tumor deposits and a total volumetric quantification of disease using manual annotation or machine learning could help to better understand how disease burden impacts risk for irAEs in an organ.

Additionally, factors including comorbidities, underlying genetic predisposition, tumor characteristics, and other potential unmeasured confounders may impact irAE risk. It is notable that all patients in our study were hospitalized with an irAE affecting at least one organ. Our study established a novel correlation between tumor

A

	No Hepatitis	Hepatitis
No Liver Tumor	270	26
Liver Tumor	72	16

B

	No Pneumonitis	Pneumonitis
No Lung Tumor	150	7
Lung Tumor	196	23

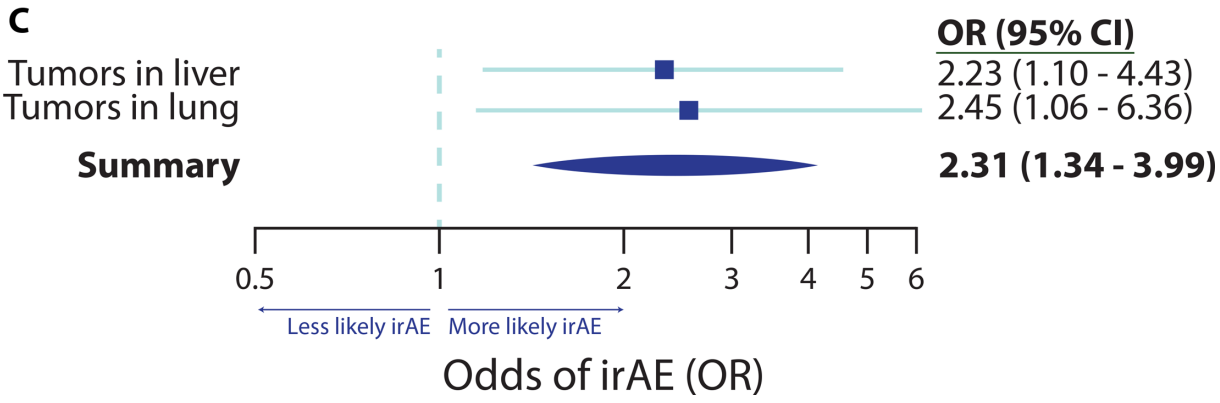

Figure 3 irAEs in livers and lungs with tumors. (A), (B) 2×2 tables of tumors and irAEs in the (A) liver and (B) lung. In each group, the patients with and without tumors in that organ and with and without a diagnosis of (A) ICI-related hepatitis and (B) ICI-related pneumonitis are shown. (C) A meta-analysis using a random-effects model of the risk of irAEs in these individual organs shows that the presence of tumor in an organ was associated with an increased risk of developing an irAE in that organ. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

location and local irAEs, but the causative factors driving this phenomenon are currently unknown. This damage could occur through the local release of inflammatory cytokines that lead to non-specific injury in local tissues, or these local inflammatory signals could lead to establishing a break in peripheral tolerance. Future prospective studies should test risk-stratifying biomarkers, clinical risk algorithms, interventions, and outcomes in patients with tumors and irAEs in the same organ. A deeper understanding of the mechanisms and clinical features driving organ-specific irAEs in patients may help to determine if irAEs driven by local tumor infiltration are a distinct endotype of irAEs.

CONCLUSION

In a pan-cancer retrospective cohort, the presence of radiographically evident tumor infiltration in the lung or liver was a significant risk factor for the clinical presentation of severe irAEs requiring hospitalization in the respective organ. Clinicians should consider tumor infiltration when monitoring and managing patients with known metastatic disease for potential irAEs.

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Collaborators Not applicable.

Contributors SMB and BO designed the study and drafted the initial manuscript. SMB, BO, LZ, DL, MW, KG, NH, GM, NS, KLR, and RJS helped to build and annotate the patient database and cases. BO performed the statistical analysis with the guidance of KS, DL, MD, A-CV, KLR, and RJS provided guidance on project design and hypothesis testing. MMK identified pathological cases and provided expert support. All authors reviewed the manuscript. RJS is the guarantor of this work.

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Patient consent for publication IRB protocol approval was obtained as above, and no patient identifiers are used.

Ethics approval This study involves human participants and was approved by Mass General Brigham Institutional Review Board protocol 2017P000501.The study used anonymized data and was exempt from obtaining individual consent per our IRB approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Source code is provided as a Supplementary File to this submission. This file is intended for review purposes only; upon acceptance of a manuscript for publication, we would deposit this code in Zenodo and make it freely available with a persistent link. A link to this code would be included in the Methods and/or Data Availability statement of any published manuscript. Upon publication, anonymized patient level data would be available upon completion of a data use agreement.

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