Radiographic Profiling of Immune-Related Adverse Events in Advanced Melanoma Patients Treated with Ipilimumab


Abstract

Ipilimumab is a promising novel immunotherapy agent and is associated with a variety of immune-related adverse events (irAE). The purpose of this study was to investigate the manifestations of irAEs on body imaging in patients with advanced melanoma treated with ipilimumab. One-hundred forty-seven patients with advanced melanoma (59 women, 88 men; median age, 64.5 years) treated with ipilimumab were studied. All patients had the baseline and at least one follow-up chest/abdomen/pelvis CT or PET/CT during therapy, which were reviewed by a consensus of two radiologists blinded to the clinical data. Findings indicative of individual types of irAEs were assessed, including thyroiditis, sarcoid-like lymphadenopathy, pneumonitis, hepatitis, pancreatitis, and colitis. Among the 147 patients, 46 (31%) had radiologically identified irAEs. The time interval from the initiation of therapy to the development of irAEs was less than 3 months in 76% (35 of 46) of the patients (range, 0.2–9.1 months). Clinical characteristics did not differ between patients with and without irAEs (P > 0.18). Among the individual types of irAEs, colitis was most common (n = 28; 19%), followed by sarcoid-like lymphadenopathy (n = 8; 5%) and pneumonitis (n = 8; 5%). Hepatitis (n = 3), thyroiditis (n = 2), and pancreatitis (n = 1) were less common. The resolution of irAEs was noted in 32 of 36 patients (89%) with further follow-up scans, with a median time of 2.3 months after the detection of irAE. In conclusion, irAEs were noted on body imaging in 31% of patients with melanoma treated with ipilimumab. Colitis was the most common, followed by sarcoid-like lymphadenopathy and pneumonitis. The results call for an increased awareness of irAEs, given the expanding role of cancer immunotherapy.

Introduction

Ipilimumab is an immune checkpoint inhibitor that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) and augments T-cell immune response against cancer cells (1–6). Following the demonstration of survival benefit and safety profile of ipilimumab in phase III clinical trials, it was approved by the FDA in March 2011 for the treatment of metastatic melanoma (1, 7). The success of ipilimumab in metastatic melanoma has led to the development of other immunotherapeutic agents, such as the inhibitors of programmed cell death receptor 1 (PD-1) and its ligand, PD-L1 (8–10), which have demonstrated marked clinical activity in advanced melanomas and other solid and hematologic malignancies, resulting in the recent FDA approvals of two different anti-PD-1 antibodies, pembrolizumab and nivolumab, for the treatment of patients with melanoma or squamous cell carcinoma of the lung (12–17).

Consistent with its mechanism of action as an immunomodulator, ipilimumab has unique side effects, which have been referred to as immune-related adverse events (irAE; refs. 18–21). The irAEs during ipilimumab therapy may involve various organs, including the colon, skin, liver, pancreas, as well as endocrine organs, such as the pituitary, thyroid, and adrenal glands (22). Most of the reports on irAEs are based on the results of phase II and III trials that used various doses of ipilimumab (0.3–10 mg/kg), with limited radiologic descriptions (23). The largest radiology series of irAEs included 81 patients treated with ipilimumab at a trial dose of 10 mg/kg and 38 patients treated in a trial of tremelimumab, another investigational agent that blocks CTLA-4 (21).

Imaging is a key component for monitoring patients during ipilimumab therapy, both for antitumor activity assessment and for workup of immune-related toxicity, thus allowing the detection of radiologic manifestations of different types of irAEs. Many of the organ-specific irAEs can be diagnosed on cross-sectional imaging of the chest, abdomen, and pelvis. Early diagnosis of irAEs is essential for prompt patient management and adequate therapeutic decisions. The role of imaging in the identification and monitoring of irAEs is becoming more important in the clinical setting, given the recent accelerated approvals of immunotherapeutic agents for different types of tumors. However, the concept of irAEs and their currently limited radiologic descriptions present challenges for prompt and accurate imaging diagnosis of irAEs. It is therefore critical to systematically document the radiographic features of irAEs that can be identified on routine body imaging during ipilimumab therapy.

The purpose of this study is to investigate the frequency of radiographically evident irAEs in patients with advanced...
Materials and Methods

 Patients

 The original cohort included 162 consecutive patients with advanced melanoma who were treated with ipilimumab monotherapy as part of the standard clinical care between April 2011 and September 2014 at the Dana-Farber Cancer Institute (Boston, MA). Among the original cohort, 147 patients (59 women, 88 men; median age, 46.5 years) had baseline and at least one follow-up cross-sectional imaging study [chest, abdomen, and pelvis CT or whole-body 18F-FDG PET/CT (FDG-PET/CT)] during therapy that were available for review, were considered to be eligible for this radiographic study, and were included in the study population. The remaining 15 patients were excluded because of a lack of available imaging studies for review. The histopathology of melanoma was confirmed in all patients. The standard clinical treatment included 4 cycles of ipilimumab at a dose of 3 mg/kg.

 The demographics and clinical characteristics of the patients were obtained by review of medical records (performed by S.H. Tirumani and A. Keraliya). This retrospective study was approved by the Institutional Review Board with waiver for informed consent and was in compliance with the Health Insurance Portability and Accountability Act.

 Cross-sectional imaging and analysis

 CT scan of the chest, abdomen, and pelvis used a 64-row MDCT scanner, with intravenous contrast agent unless medically contraindicated. Axial (5-mm thickness) and coronal (4-mm thickness) images were transferred to the Picture Archiving Communication System (PACS; Centricity; GE Healthcare). Whole-body PET imaging was performed approximately 60 minutes after i.v. administration of 18F-FDG. Noncontrast CT imaging was performed without breath-hold, and axial images (3.75–5 mm thickness) were transferred to PACS. The median time between the baseline scan and initiation of ipilimumab monotherapy was 0.7 months (range, 0–2.5 months). Follow-up scans were performed at the treating clinical providers’ discretion, without predefined intervals.

 The images were reviewed by consensus of two board-certified radiologists (M. Nishino, N.H. Ramaiya) with expertise in cancer imaging. A total of 748 CT and 326 PET/CT scans were reviewed (median number of scans per patient, 5). Radiologists were aware that the patients were treated with ipilimumab for advanced melanoma; however, the radiologists did not have access to other clinical details. For each patient, the baseline and follow-up scans were reviewed to identify the development of predefined imaging findings indicative of irAEs, based on the descriptions in the existing literature (21, 24–28).

 The organ-specific irAEs evaluated in the present study included thyroiditis, sarcoid-like lymphadenopathy, pneumonitis, hepatitis, pancreatitis, and colitis. The imaging criteria for each of the irAEs are as follows: (i) thyroiditis: new enlargement of the thyroid gland with heterogeneous enhancement or new diffuse FDG uptake on PET; (ii) sarcoid-like lymphadenopathy: new bilateral symmetric mediastinal and hilar lymphadenopathy resembling typical sarcoidosis without evidence of infection, not suspicious for metastasis and occurring in the setting of response at other sites (21, 29–31); (iii) pneumonitis: new consolidative or ground glass opacities with distributions and appearances that are not consistent with metastasis (24, 28); (iv) hepatitis: hepatomegaly, heterogeneous parenchymal enhancement with low-attenuation areas, periperal/gall bladder edema (26); (v) pancreatitis: new focal or diffuse pancreatic enlargement with decreased enhancement and peripancreatic stranding, without a focal lesion suspicious for metastasis (32); and (vi) colitis: fluid-filled colon, mesenteric vessel engorgement, bowel wall thickening (>4 mm irrespective of distension), or increased mucosal enhancement on contrast-enhanced CT scan of the abdomen (27, 33). The cases of colitis were classified into two subtypes: (i) diffuse pancolitis and (ii) segmental colitis associated with diverticulosis (SCAD) restricted to a segment of colon with diverticulosis (27).

 For each of the irAEs, a score was given by a consensus using a 5-point scale: 1, definitely not irAE; 2, probably not irAE; 3, equivocal; 4, probably irAE; and 5, definitely irAE. Cases with scores of 4 and 5 were considered as positive for irAEs. The date of the first scan that scored 4 or 5 for the irAEs was used to represent the onset of radiographically evident irAEs. Subsequent follow-up scans, if available, were reviewed to assess resolution of the radiographic findings.

 After the completion of the imaging review, cases with radiographically evident irAEs were correlated with clinical, biochemical, or histopathologic assessments, collected by review of medical records by S.H. Tirumani and A. Keraliya.

 Statistical analysis

 Differences in demographics and clinical characteristics were compared between patients with and without radiographically evident irAEs, using the Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. The median time to development of radiographically evident irAEs was calculated using the Kaplan–Meier method, and patients who did not develop radiologically identified irAEs were censored at the time of last follow-up imaging. All P values were based on a two-sided hypothesis. P < 0.05 was considered to be statistically significant.

 Results

 Overall frequency and characteristics of radiographically evident irAEs

 Among the 147 patients with advanced melanoma treated with ipilimumab, 46 patients (31%) developed radiographically evident irAEs. Radiologic irAEs were noted within 3 months from the initiation of therapy in 35 (76%) of the 46 patients (range, 0.2–9.1 months; Fig. 1). No statistically significant differences were observed between the two groups (P > 0.18), including the median duration of ipilimumab therapy (P = 0.61; Table 1).

 Further follow-up scans after the onset of radiographically evident irAEs were available in 36 patients (89%). Eventual resolution of the radiographic findings was noted in 32 of the 36 patients; 22 of the 32 patients (69%) had resolution within
was also noted in 6 patients. Twenty-six patients had a diffuse colitis pattern (Fig. 2), and 2 patients had a SCAD pattern. Of the 28 patients, diarrhea (4–12 episodes/d) was noted in 25 patients, and 3 patients had nonspecific abdominal pain without diarrhea. Colonoscopy and biopsy were performed in 22 patients, confirming colitis, which was thought to be consistent with ipilimumab-associated colitis given the clinical setting. Oral steroids were given as a treatment of colitis for 23 patients, and 11 of them also received infliximab. Surgery was performed in 3 patients with colonic perforation.

Further follow-up scans were available in 21 patients. In 20 patients, the resolution of colitis was noted with a median interval from onset to resolution of 1.8 months (range, 0.3–8.0 months). In 1 patient, the findings of colitis continued at the last follow-up imaging performed 3 months after onset.

**Sarcoid-like lymphadenopathy.** Sarcoid-like lymphadenopathy was seen in 8 patients, demonstrating newly enlarged mediastinal and hilar nodes (n = 5), enlargement of preexisting nodes (n = 1), and both new and enlarged nodes (n = 2). The median interval from the initiation of ipilimumab therapy was 3.2 months (range, 0.2–9.1 months; Figs. 3 and 4). Coexistent pulmonary findings were also noted in 3 patients, including irregular nodular and parenchymal opacities with bilateral symmetric involvement predominantly in the upper and middle lungs (n = 1), bilateral diffuse ground glass opacity with upper and middle lung predominance (n = 1), and bilateral peripheral interstitial opacities in the lower lobes with pleural effusion (n = 1). Coexistent intra-abdominal lymphadenopathy was noted in 1 patient.

Sarcoid-like lymphadenopathy was not associated with clinical signs or symptoms in any of the patients. None of the patients had a history of sarcoidosis or hypercalcemia or evaluation of serum angiotensin-converting enzyme (ACE). Follow-up scans were available in 6 patients, showing the resolution of lymphadenopathy in all of them, with a median interval to resolution of 3.1 months (range, 1.1–5.4 months).

**Pneumonitis.** Pneumonitis was noted in 8 patients, with a median time from the initiation of therapy to the onset of 2.3 months (range, 1.1–8.3 months). CT findings included bilateral consolidative and ground glass opacities predominantly in peripheral

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**Table 1. Demographics and clinical characteristics**

<table>
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<tr>
<th>Characteristics</th>
<th>With irAE (n = 46)</th>
<th>Without irAE (n = 101)</th>
<th>Total (N = 147)</th>
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<td>8.0</td>
<td>8.1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

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**Figure 1.**

The cumulative probability of radiographically evident irAEs during ipilimumab therapy.
Pancreatitis was noted in 1 patient at 3.8 months of therapy, shown by pancreatic enlargement with a decreased enhancement and surrounding fat stranding on CT and an increased FDG uptake on PET. The patient was clinically asymptomatic for pancreatitis; however, the elevation of the serum amylase (×10) and lipase (32-fold) was noted at the time of positive imaging finding. The pancreatitis radiographically resolved 6.5 months after onset without any specific treatment. The patient also had immune-related hypophysitis diagnosed clinically 2 months prior to the onset of pancreatitis.

**Discussion**

The irAEs were noted on body imaging in 31% (46 of 147) of patients with advanced melanoma treated with ipilimumab and occurred within 3 months after the initiation of therapy in the majority of patients (76%, 35 of 46). Colitis was the most common organ-specific irAE, followed by sarcoid-like lymphadenopathy and pneumonitis. In most of the cases of irAEs (89%), the radiologic findings resolved on the subsequent follow-up imaging at a median interval of 2.3 months. The high incidence of irAEs and their variable manifestations on body imaging involving different organs are provocative for the important role of imaging in diagnosis and monitoring of this emerging entity, in the new and expanding arena of cancer immunotherapy.

In the phase III trial of metastatic melanoma, the incidence of any irAE in 131 patients treated with ipilimumab monotherapy was 61% (1, 19), with dermatologic irAEs being the most common manifestation, occurring in 43.5% of patients. Dermatologic irAEs were not evaluated in the present study focusing on...
radiographic abnormalities, explaining the lower incidence of irAEs noted on body imaging (31%). On the other hand, the incidence of irAEs in the present study was higher than that in the previous radiologic report by Bronstein and colleagues, based on their study of 119 patients (81 treated with ipilimumab and 38 treated with tremelimumab) and identified 20 patients (16.8%) with radiologic abnormalities potentially explained by irAEs (21).

Several differences between the two studies could account for the difference. First, the 147 patients in the present study were all treated with ipilimumab monotherapy, whereas the Bronstein study included two subcohorts treated with different agents in different trial protocols. Second, the present study provided the predefined radiologic findings indicative of organ-specific irAEs in six different organs for radiology review, based on the descriptions of the reports focusing on the individual types of irAEs published between 2012 and 2014 (19, 20, 26–29, 34), which was not available at the time of the report by Bronstein and colleagues, published in 2011 (21). The present study evaluated irAEs not described in the Bronstein study, including pneumonitis, hepatitis, and pancreatitis; The Bronstein study described hypophysitis, arthritis, myositis, and retroperitoneal fat opacities that are not included in the present study. The different approaches and different results are also indicative of the rapidly evolving knowledge of treatment effects and adverse events associated with cancer immunotherapy.

In 76% of the patients in the present study, radiographic irAEs were noted within 3 months after the initiation of therapy; this is consistent with the detailed analysis of the data from the phase III trial of ipilimumab conducted by Weber and colleagues, which showed that a substantial number of irAEs occurred within the first 12 weeks of treatment (19). Radiologic findings of irAEs resolved in 89% of the patients with follow-up imaging in the present study, with a median interval of 2.3 months, which is in line with the time frame of 6 to 8 weeks reported by Weber and colleagues (19). Our study has a slightly longer time to resolution, which may be because the timing of resolution is subject to the timing of follow-up imaging, whereas the resolution of many clinical irAEs can be noted by clinical evaluations that occur more frequently.

Colitis was the most common organ-specific irAE, seen in 19% (28 of 147) of patients. The incidence of gastrointestinal irAEs varies between 31% and 46% in the clinical studies, with grade 3 or higher colitis occurring in 10% and 23% of patients (19, 22, 35, 36). In a report by Weber and colleagues, gastrointestinal irAEs were the second most common after dermatologic irAEs, noted in 29% (38 of 131) of patients, manifesting as diarrhea (27.5%; 36 of 131) and/or colitis (7.6%; 10 of 131; ref. 19). The incidence of colitis as an irAE in the present study mostly falls within the ranges of incidence described in the prior clinical studies. The small differences can be explained by the differences between the definitions of radiographic colitis and the definitions of clinical gastrointestinal irAEs, including the spectrum of diarrhea and colitis. Ipilimumab-associated colitis has been reported to typically develop 6 to 7 weeks after the initiation of therapy and resolve within 6 to 8 weeks (19), which is consistent with our radiologic results, further confirming the clinical utility of the imaging evaluations used in the present study based on the previous report (27).
was more common than SCAD, consistent with the prior report (27). Prompt diagnosis of colitis in patients treated with ipilimumab is critical because it can lead to serious complications such as bowel perforation if left untreated. Among a cohort of 643 patients in the phase III trial, 5 deaths were associated with colitis and its complications (19).

Sarcoid-like lymphadenopathy is an underreported ipilimumab-related irAE, although it is described in a few sporadic studies (25). The incidence of sarcoid-like lymphadenopathy in our study (5%) was similar to that reported by Bronstein and colleagues (6.7%, 8 of 119; ref. 21). Three patients in our series also had concurrent pulmonary parenchymal changes that are within the spectrum seen in pulmonary sarcoidosis (37, 38), as described in a previous report (25). Some cases of sarcoid-like lymphadenopathy can be clinically silent and incidentally noted on imaging, as in the 8 cases in the present study, leading to underdocumentation in the clinical literature. Because new lymphadenopathy also raises concern for metastatic diseases, the awareness of sarcoid-like lymphadenopathy as a manifestation of irAEs is essential in achieving accurate diagnosis and management, and in directing the patient to adequate clinical testing, such as serum ACE level assessments. Sarcoid-like lymphadenopathy resolved in all the patients with follow-up scans in our study, further confirming the benign nature of the process.

Pneumonitis during ipilimumab therapy is described in a few clinical case reports and in a phase II trial conducted by the Eastern Cooperative Oncology Group, in which 7.5% (9 of 120) of the patients treated with ipilimumab monotherapy at a dose of 10 mg/kg developed pulmonary toxicity (24, 28, 39). However, the detailed radiologic description of this entity is limited. Among the 8 patients in the present study, the radiologic manifestations mimicked the COP pattern in 5 patients, as in the prior report (24), and the remaining 3 patients had findings resembling an NSIP pattern, which has been known to be associated with conventional agents such as methotrexate and carmustine (40). The characterization of this irAE may be of increasing importance, given that anti–PD-1/PD-L1 antibodies are known to be associated with clinically significant, potentially lethal immune-related pneumonitis (41). The attention to the pulmonary findings described here may also be particularly important in the setting of combination therapy using ipilimumab plus anti–PD-1 antibodies or other agents that are being tested (42–44). Further studies are needed to fully characterize the spectrum of drug-related pneumonitis during cancer therapy.

Hepatic irAEs related to CTLA-4 inhibition are less common than gastrointestinal or dermatologic irAEs in trials. A post hoc clinical review by Weber and colleagues identified 5 patients with grade ≥3 hepatic irAEs among 511 ipilimumab-treated patients (19). The relatively low incidence (2%) of hepatitis on imaging is similar to the clinical report given it focused on grade ≥3 toxicity. Although less common, a potential severe clinical implication is noted in a prior study in which one death was attributed to liver failure due to irAE during ipilimumab monotherapy (19), further emphasizing the clinical significance of prompt diagnosis.

Endocrine irAEs were relatively common after dermatologic and gastrointestinal irAEs in the phase III trial of ipilimumab, noted in 7.6% (10 of 131) of patients with melanoma treated with ipilimumab monotherapy (1, 19). Hypothyroidism was seen in 2 patients (1.5%), which is similar to the incidence in the present study. The imaging features in 2 patients in the present study were new diffuse FDG uptake in the thyroid gland, which raises the possibility of underdiagnosis among those without PET imaging.
Immune-related pancreatitis has been reported as a relatively rare manifestation of irAEs (45, 46). In a retrospective study of a cohort of 39 patients with uveal melanoma, 1 patient (2.5%) had ipilimumab-associated pancreatitis (46). Pancreatitis can be asymptomatic with an elevation of serum amylase and lipase alone, as in the case detected in the present study, or it can be associated with nonspecific symptoms (32). Imaging plays an important role in detecting this rare entity in the presence of the pertinent imaging findings somewhat simulating autoimmune pancreatitis in the relevant clinical setting.

The limitation of the present study includes a retrospective design in the cohort treated at a single institution; however, this cohort is larger than the cohorts treated with single-agent ipilimumab in previous radiology or clinical studies (1, 19, 21, 46) and represents the first cohort of patients with advanced melanoma treated with ipilimumab monotherapy outside of clinical trials undergoing systematic review of body imaging studies for irAEs. Because the patients were treated clinically without being enrolled in prospective trials, scans were performed according to the clinical care provider’s discretion without predefined intervals, which limits the detailed analysis of sensitivity for irAEs across different image modalities. Although hypophysitis is a known endocrinologic irAE, it was not included in the present study, which focused on six different types of irAEs noted on body imaging. The entity is well described in the endocrinology literature (47–50), and a detailed neuroradiologic investigation is planned. Not all the cases of radiologically detected irAEs had histologic confirmation, which is often the case with cohorts of patients with advanced malignancy. Clinical confirmation was not obtained in some cases, partly because some irAEs, such as sarcoid-like lymphadenopathy, are known to be clinically silent. Of note, irAEs consist of a variety of entities involving different organs with emerging and evolving concepts, which led to the study design not requiring clinical confirmation for all positive cases. Instead, the predefined imaging features for each organ-specific irAE based on the published literature were used to guide the systematic radiology review. Given the emerging clinical and radiologic concept of irAEs, it is currently difficult to define the absolute ‘gold standard’ for the diagnosis of irAEs; rather, the diagnosis often requires the interplay among clinicians, radiologists, and sometimes pathologists via their multidisciplinary interactions. Therefore, no formal assessments of the sensitivity and specificity of radiologic diagnosis of irAEs were performed.

In conclusion, radiographically evident irAEs on body imaging were present in nearly one third of patients with advanced melanoma treated with ipilimumab monotherapy as standard of care, based on the longitudinal systematic review of their imaging studies. Among the organ-specific irAEs, colitis was most common, followed by sarcoid-like lymphadenopathy and pneumonitis. The high incidence of irAEs and the imaging manifestations in various organs call for the awareness of this emerging entity, given the expanding roles and applications of cancer immunotherapy in clinical oncology practice.

Disclosure of Potential Conflicts of Interest
F.S. Hodi reports receiving commercial research support from Bristol-Myers Squibb, has ownership interest in a pending patent on MICA antibodies, and is a nonpaid consultant for Bristol-Myers Squibb. M. Nishino is a consultant/advisory board member for Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

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Development of methodology: M. Nishino
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.H. Tirumani, N.H. Ramaiya, F.S. Hodi, M. Nishino
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N.D. Bailey
Study supervision: N.H. Ramaiya

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