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Cancer Immunotherapy: Imaging Assessment of Novel Treatment Response Patterns and Immune-related Adverse Events[1]

Jennifer J. Kwak, MD
Sree Harsha Tirumani, MD
Annick D. Van den Abbeele, MD
Phillip J. Koo, MD
Heather A. Jacene, MD

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte antigen–4, FDA = U.S. Food and Drug Administration, FDG = fluorodeoxyglucose, MIP = maximum intensity projection

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[1]From the Department of Radiology, University of Colorado School of Medicine, Anschutz Medical Campus, 12700 E 19th Ave, Room C278, Aurora, CO 80045 (J.J.K., P.J.K.); and Department of Imaging, Dana-Farber Cancer Institute, and Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (S.H.T., A.D.V.d.A., H.A.J.). Presented as an education exhibit at the 2013 RSNA Annual Meeting. Received March 24, 2014; revision requested July 11 and received September 2; accepted September 4. For this journal-based SA-CME activity, the authors P.J.K. and H.A.J. have provided disclosures (see p 436); all other authors, the editor, and the reviewers have disclosed no relevant relationships. **Address correspondence to** J.J.K. (e-mail: *jen.j.kwak@gmail.com*).

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Provide examples of cancer immunotherapy.
- Describe the four patterns of cancer immunotherapy treatment responses observed after immunomodulatory therapy.
- List the immune-mediated adverse events associated with immunomodulatory therapy at posttreatment imaging.

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Cancer immunotherapy is changing the imaging evaluation of cancer treatment response and treatment-related toxic effects. New emerging patterns of treatment response and treatment-related toxic effects after treatment with immunomodulating agents have been observed. Treatment response after immunomodulatory therapy can be associated with significantly delayed decrease in tumor size, and new or enlarging tumors observed soon after completion of treatment may not reflect disease progression. In addition, activation of the immune system to fight cancer may lead to unwanted autoimmune-mediated toxic effects that could be mistaken for metastatic disease or misdiagnosed as a non–treatment-related process and delay appropriate clinical management. Radiologists must recognize the novel treatment response patterns and the wide range of autoimmune toxic effects, which should not be mistaken for treatment failure or metastatic disease progression.

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Introduction

Cancer immunotherapy utilizes the passive or active immune responses of the immune system to treat cancer. In contrast to traditional cancer treatment modalities, which remove cancer cells by surgery or kill cancer cells with radiation or cytotoxic chemotherapy, cancer immunotherapy can elicit the immune system to remove or kill cancer cells.

Passive cancer immunotherapy has already become an established treatment modality for select cancers. In passive cancer immunotherapy, patients receive preformed antibodies that are directed against tumor-associated antigens and that bind to their targets, resulting in clearance of the antigens by the immune system.

TEACHING POINTS

- Active cancer immunotherapy modulates the immune system by activating both cell-mediated and humoral immunity to fight cancer.
- Under normal conditions, this negative regulatory mechanism functions to prevent autoimmunity. However, in the setting of active immune response to cancer, CTLA-4 inhibitors prevent inhibition of the activated T-cells that are primed to attack cancer cells and allow the immune system to continue killing cancer cells.
- Early clinical experience with recombinant cytokines, cancer vaccines, and immunomodulatory monoclonal antibodies has demonstrated a delayed response to treatment compared with cytotoxic chemotherapy, clinically significant disease stability, and transient enlargement of tumors or the appearance of new tumors followed by shrinkage of tumor or long-term stability of tumor size.
- Key points of the immune-related response criteria are as follows: *(a)* Because of a potentially delayed response to immunotherapy treatment, imaging assessment of treatment response or disease progression after completion of treatment should be made with two consecutive follow-up imaging studies performed at least 4 weeks apart, and *(b)* unlike with previous solid tumor response criteria, new or enlarging lesions do not necessarily represent progression of disease immediately after completion of treatment. Because of this, follow-up imaging should be performed at least 4 weeks later to assess for further changes in tumor burden.
- It is important for the imager to recognize the unique adverse events associated with immunotherapy to guide appropriate treatment and avoid potential imaging pitfalls that could be mistaken for metastatic progression of disease.

Active cancer immunotherapy is an emerging treatment modality that can harness the adaptive response of the immune system to kill cancer cells that attempt to evade the immune system. This new immunomodulatory approach to cancer treatment comes with new patterns of treatment response and treatment-related toxic effects that were not previously seen with traditional cytotoxic chemotherapy.

The success of traditional cytotoxic chemotherapy depends on prompt decrease in size of known tumors and the absence of new tumors. Unlike treatment response after traditional cytotoxic chemotherapy, treatment response after immunomodulatory therapy can be associated with an initial delay in response to treatment, including a slow decrease in tumor size and the appearance of new or enlarging tumors immediately after treatment that eventually resolve or decrease in size over time, without further treatment.

In addition, active cancer immunotherapy can result in unwanted activation of autoimmunity, resulting in a wide range of toxic effects. If not appropriately recognized, these treatment-related autoimmune toxic effects may be mistaken for metastatic disease progression or misdiagnosed as an infectious or inflammatory process, resulting in delayed treatment, which could lead to more serious complications. In this article, we review the important concept of cancer immunotherapy and discuss immune-related response patterns and immune-related adverse events, with multimodality imaging examples given to help radiologists accurately interpret postimmunotherapy images.

Cancer Immunotherapy

Cancer immunotherapy was developed on the basis of the concept of immune surveillance. During immune surveillance, the immune system is responsible for early detection of abnormal cells and development of an appropriate antitumor response to remove cancer cells (1). The immune system mounts an antitumor response by detecting tumor-associated antigens; this ability is evidenced by the presence of tumor antigen antibody titers in cancer patients (1). However, the body is not able to generate a sufficient antitumor response because cancer cells can evade detection by the immune system and inhibit antitumor immune response, allowing them to grow and metastasize in the body.

Accordingly, the goal of cancer immunotherapy is to boost the immune system to allow it to mount a more effective antitumor response. Currently available cancer immunotherapies are divided into two broad categories on the basis of the immune response elicited by the treatment: passive immune response and active immune response.

Passive immune response requires no activation of the immune system. With passive cancer immunotherapy, preformed antitumor immunoglobulins made outside the body are passively infused into the patient, and the binding of antitumor immunoglobulins to tumor-associated antigens triggers clearance of the tagged tumor cells by the immune system. In contrast, active immune response is mediated by the immune system with a humoral and/or cell-mediated immune response to cancer cells. Active cancer immunotherapy enhances the immune system to actively respond by producing antitumor antibodies, recruiting scavenger immune cells that seek out and kill cancer cells, and prompting the release of cytokines that further enhance the active response to cancer cells.

Passive Cancer Immunotherapy

Passive immunotherapy for cancer has become a well-established treatment. Preformed monoclonal antibodies directed against known cancer-associated proteins are used to treat cancer and include trastuzumab, which is directed

against human epidermal growth factor receptor 2 (HER2)/*neu*; bevacizumab, which is directed against vascular endothelial growth factor (VEGF); and rituximab, which is directed against the CD20 antigen (1,2).

Preformed monoclonal antibodies inhibit cancer cell growth by blocking receptor sites and signaling proteins and induce cancer cell death by tagging cancer cells for removal by the immune system (1,2). For example, bevacizumab binds to VEGF and inhibits cancer growth by blocking angiogenesis, and rituximab treats lymphoma by binding to the CD20 protein on the surface of lymphocytes and induces cell death by activating the complement and cell-mediated cytotoxic immune response (1). Preformed monoclonal antibodies have also been used to deliver tumor-targeted cytotoxic chemotherapy or radiation therapy (1).

Unfortunately, cancer cells can develop resistance to passive antibody therapies by losing or decreasing the expression of the targeted tumor antigens. An approach to counter the development of resistance to therapy over time is to use the active immune response, which can potentially detect and adapt to changes in the tumor, thereby preventing tumor escape from the immune system (3).

Active Cancer Immunotherapy

Active cancer immunotherapy modulates the immune system by activating both cell-mediated and humoral immunity to fight cancer (4). Currently used active cancer immunotherapy treatments include recombinant cytokines, biochemotherapy, vaccinations, and immunomodulatory monoclonal antibodies (5).

Recombinant cytokines approved for use by the U.S. Food and Drug Administration (FDA) are interleukin-2 (IL-2) and interferon-α (IFN-α). Cytokines have been used for treatment of melanoma, renal cell carcinoma, lymphoma, chronic myelogenous leukemia, and Kaposi sarcoma (1). IL-2 and IFN-α stimulate T-cell proliferation and function, augment natural killer cell activity, and trigger the release of additional proinflammatory cytokines from activated lymphocytes (5–7). Toxicity often limits treatment duration and limits treatment to a select group of patients.

Biochemotherapy is the combination of traditional cytotoxic chemotherapy agents and recombinant cytokines (7). A recombinant cytokine, IL-2 or IFN-α, is concurrently administered with a single chemotherapy agent or a combination of chemotherapy agents, including dacarbazine, cisplatin, vinblastine, and temozolomide (5,7). Use of biochemotherapy can improve the active immune response of recombinant cytokines by combining the immune response generated by cytokines with cancer cell damage caused by cytotoxic agents, which exposes larger numbers of tumor antigens for detection by the immune system. For example, in the treatment of metastatic melanoma, biochemotherapy has been shown to have higher response rates than chemotherapy or recombinant cytokines alone; however, the improved response rate comes at the cost of increased toxicity compared with single-agent treatment, and there is no proven significant survival benefit (5).

Vaccines have also been used to trigger an active immune response against cancer. Currently, the only vaccine that is FDA-approved for cancer treatment is sipuleucel-T, which was approved in April 2010 for treatment of metastatic prostate cancer. Additional cancer vaccines have been used in clinical trials for melanoma, renal cell carcinoma, bladder cancer, glioblastoma, breast cancer, lung cancer, pancreatic cancer, and colon cancer (1,8).

Immunomodulatory monoclonal antibodies are the newest active cancer immunotherapy agents. These immunomodulators epitomize the goal of active cancer immunotherapy by directly targeting the T-cells involved in cell-mediated adaptive immune response. In addition, the antitumor response and associated treatment-related complications associated with this emerging new active cancer immunotherapy highlight the important differences between posttreatment imaging assessment of cancer immunotherapy and traditional cytotoxic chemotherapy.

Immunomodulatory Monoclonal Antibody Therapy

Immunomodulatory monoclonal antibody therapy utilizes preformed monoclonal antibodies directed against molecular targets on the surface of T-cells to regulate T-cell activation. Although preformed monoclonal antibodies are used, the end result is direct activation of the adaptive immune response by modulating T-cell function, unlike with passive immunotherapy. Much of the early research in development of active cancer immunotherapy has been performed in the treatment of melanoma and renal cell carcinoma.

Ipilimumab is the first FDA-approved immunomodulatory monoclonal antibody (6). In March 2011, ipilimumab was approved for treatment of metastatic and unresectable melanoma, becoming the first new drug approved in 13 years for treatment of metastatic disease and the first drug to be approved by the FDA on the basis of phase III clinical trials demonstrating improved overall survival (6,9). Ipilimumab is a weight-based drug (3 mg/kg) that is intravenously

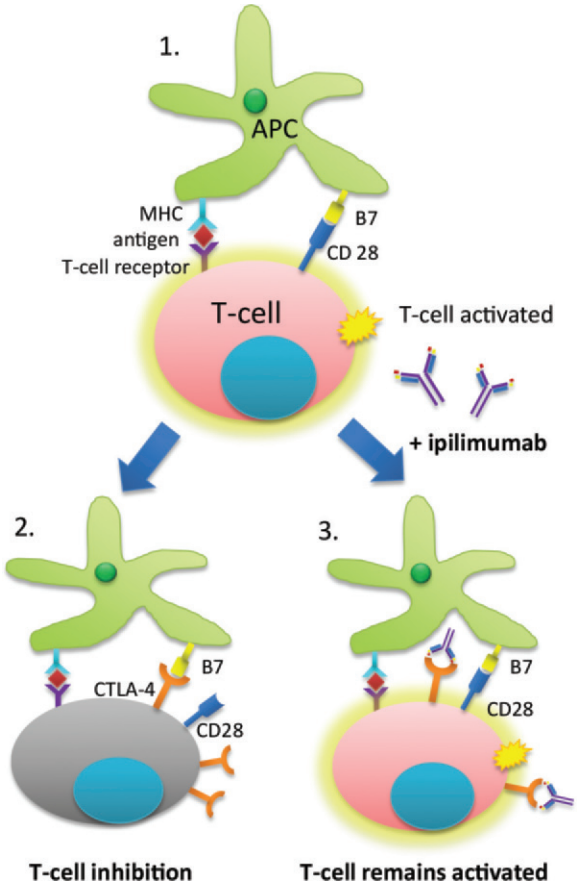


Figure 1. Illustration shows the mechanism of action of T-cell immune checkpoint inhibition. *1:* An antigen-presenting cell *(APC)* displays a tumor antigen on its cell surface major histocompatibility complex *(MHC)* molecule, which is detected by the T-cell receptor on the surface of the T-cell. Costimulatory molecule B7 on the cell surface of the APC binds to CD28 on the surface of the T-cell, and T-cell activation occurs. *2:* Activation of the T-cell results in increased expression of CTLA-4 on the surface of the T-cell. CTLA-4 outcompetes CD28 for binding of the costimulatory B7 molecule, and T-cell activation is turned off. *3:* In the presence of a CTLA-4 inhibitory monoclonal antibody, such as ipilimumab, the CTLA-4 antibody binds to CTLA-4 on the surface of the T-cell and prevents deactivation of the T-cell.

administered every 3–4 weeks over 3 months, for a total of four doses. Other immunomodulatory monoclonal antibodies that are being used in clinical trials but are not currently FDA approved include tremelimumab, which has the same T-cell molecular target as ipilimumab, and immunomodulatory monoclonal antibodies that are directed against the programmed death protein 1 (PD-1)/programmed death receptor ligand 1 (PD-L1), such as nivolumab, which targets a T-cell molecule similar to the ipilimumab target (3,6). Recently, in December 2014, nivolumab was approved for use by the FDA.

Mechanism of T-Cell Immunomodulation

As more T-cell activation regulatory pathways are being elucidated at the molecular level, more targets for modulating the immune response to cancer cells are being developed. The receptor-ligand pairs on the cell surface that are involved in regulating T-cell activation have been termed *immune checkpoints* (3). Ipilimumab is a cytotoxic T-lymphocyte antigen–4 (CTLA-4) immune checkpoint inhibitor. CTLA-4 is an important regulator of immune tolerance and one of the main negative regulators of T-cell–mediated immune response to cancer cells (6).

When a T-cell encounters an antigen on the surface of the antigen-presenting cell, the B7 costimulatory molecule on the surface of the antigen-presenting cell binds to the CD28 molecule on the surface of the T-cell, resulting in T-cell activation (Fig 1). Activated T-cells then transiently express high levels of CTLA-4 on the cell surface, which can outcompete the CD28 molecule for binding to the B7 costimulatory molecule and turn off an activated T-cell (Fig 1) (3,10). Under normal conditions, this negative regulatory mechanism functions to prevent autoimmunity (3). However, in the setting of active immune response to cancer, CTLA-4 inhibitors prevent inhibition of the activated T-cells that are primed to attack cancer cells and allow the immune system to continue killing cancer cells (Fig 1).

Novel Patterns of Treatment Response

Imaging evaluation of response to traditional cancer treatment with cytotoxic chemotherapy, radiation therapy, or surgical resection is based on a reduction in size of the tumor and the absence of new tumor in accordance with the World Health Organization criteria or the Response Evaluation Criteria in Solid Tumors (RECIST). Cytotoxic chemotherapy kills cancer cells. The

success of cytotoxic chemotherapy is measured by decreased tumor size within a few weeks of initiating treatment. As a result, in the setting of cytotoxic chemotherapy, early tumor growth or the appearance of new lesions is considered progressive disease and a treatment failure. In addition, stable tumor size after cytotoxic chemotherapy is often transient; hence, stable disease is also considered a treatment failure (4).

In contrast, early clinical experience with recombinant cytokines, cancer vaccines, and immunomodulatory monoclonal antibodies has demonstrated a delayed response to treatment compared with that of cytotoxic chemotherapy, clinically significant disease stability, and transient enlargement of tumors or the appearance of new tumors followed by tumor shrinkage or long-term stability of tumor size (4). In the longest follow-up study after treatment of metastatic melanoma with ipilimumab, the average time to achieve response in complete responders was 30 months (11).

Four patterns of treatment response after treatment with ipilimumab therapy are recognized (4). The first is a decrease in size of known tumors with no evidence of new tumors after completion of treatment. This is the traditional desired response to treatment after cytotoxic chemotherapy (Fig 2).

The second pattern of response is clinically stable disease after completion of treatment (Fig 3). Sometimes, a long period of disease stability is followed by an eventual decline in tumor burden. This delay in treatment response likely reflects the time interval during which the immune system mounts the initial response, with activation and expansion of tumor-reactive T-cells to control the tumor (3).

The third pattern is a delayed tumor response to treatment after an initial increase in tumor burden that manifests as an increase in tumor size (Fig 4). This initial increase in tumor size is thought to reflect a continued increase in the size of the tumor while the body mounts a sufficient immune response and/or a transient increase in tumor size that results from immune cell infiltration of the tumor with or without edema (4). Both explanations were confirmed with results of tumor biopsy (3,4).

The fourth pattern of response is the appearance of new lesions after the completion of treatment that precede a decrease in tumor burden at subsequent follow-up examinations. The appearance of new lesions may represent an interval increase in the size of micrometastases that were initially too small to be visualized at imaging. These micrometastases become larger and are detectable at posttreatment imaging as a result of immune cell infiltration of the tumor (4).

These new emerging patterns of treatment response after immunomodulatory therapy demonstrated the inadequacy of the World Health Organization and RECIST criteria for evaluation of solid tumors in the setting of active cancer immunotherapy. As a result, observed patterns of treatment response from phase II clinical trials of ipilimumab were used to develop the immune-related response criteria for evaluation of treatment response after immunotherapy (4).

Because clinical response to treatment may be delayed with some forms of immunotherapy, appropriate follow-up imaging is important to identify potential treatment benefits of cancer immunotherapy (12). The immune-related response criteria specifically address appropriate imaging follow-up recommendations (4). Key points of the immune-related response criteria are as follows: *(a)* Because of a potentially delayed response to immunotherapy treatment, imaging assessment of treatment response or disease progression after completion of treatment should be made with two consecutive follow-up imaging studies performed at least 4 weeks apart, and *(b)* unlike with previous solid tumor response criteria, new or enlarging lesions do not necessarily represent progression of disease immediately after completion of treatment. Because of this, follow-up imaging should be performed at least 4 weeks later to assess for further changes in tumor burden.

The immune-related response criteria do not specifically address which imaging modalities should be used in evaluation of treatment response. Anatomic (ie, CT) and combined anatomic and metabolic (ie, FDG PET/CT) imaging are used interchangeably for evaluation of treatment response. Imaging evaluation with the immune-related response criteria does not incorporate changes in tumor metabolism, which is reflected by changes in tumor FDG avidity at PET. However, immune-related adverse events may be detected earlier with FDG PET/CT and can precede clinical symptoms, allowing early therapeutic interventions.

Implementation of the immune-related response criteria is useful to avoid premature termination of effective immunotherapeutic treatments when evaluating treatment response with currently available imaging tools in clinical practice. However, efforts are under way to predict earlier treatment response by developing imaging tools that can differentiate inflammatory response from tumor proliferation. Novel PET radiotracers that incorporate amino acids, nucleotides, choline, and s-receptor ligands to depict cell proliferation or cell death are being investigated (13). In addition, investigational use of magnetic resonance (MR) imaging for depicting apoptosis and cell lysis to

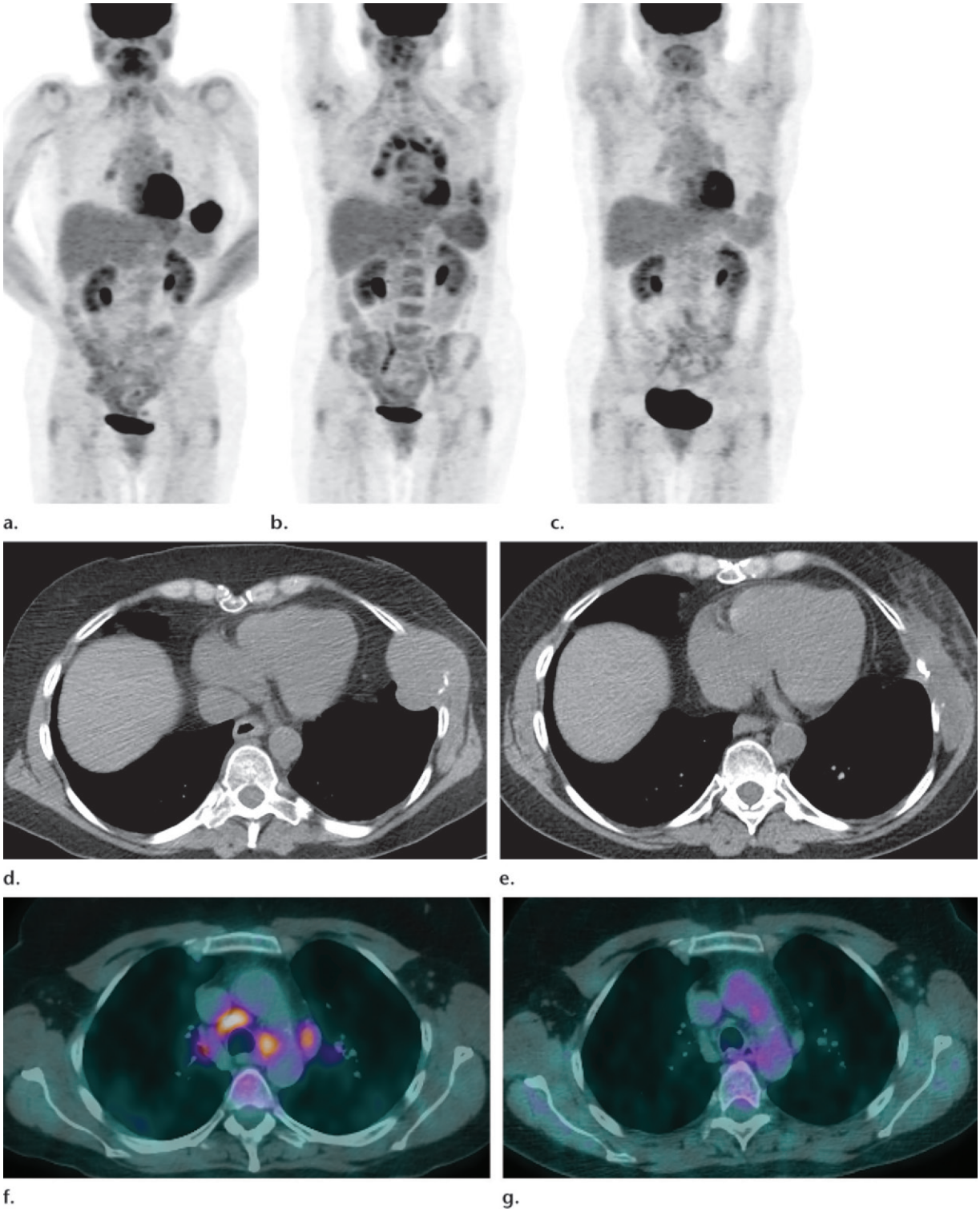


Figure 2. Complete response in a 65-year-old woman with recurrent metastatic melanoma to the left side of the chest wall. **(a–c)** Sequential maximum intensity projection (MIP) positron emission tomography (PET) images obtained before immunomodulatory monoclonal antibody treatment (ipilimumab) **(a)**, 3 weeks after completion of treatment **(b)**, and 16 months after treatment **(c)** show the treatment response of the large fluorodeoxyglucose (FDG)–avid chest wall mass. Of note, transient sarcoid-like mediastinal and hilar adenopathy developed immediately after treatment but spontaneously resolved. **(d)** Axial localization computed tomographic (CT) image obtained before treatment shows the chest wall mass. **(e)** Localization CT image obtained 16 months after treatment shows resolution of the chest wall mass. As demonstrated in **c**, inflammatory changes are indicated by mild, diffuse FDG uptake in areas of treatment-related soft-tissue thickening of the adjacent left lateral chest wall muscles. The patient demonstrated durable complete response at imaging as many as 24 months after completion of treatment. **(f)** Fused PET/CT image of the chest shows FDG-avid mediastinal lymph nodes 3 weeks after completion of treatment, a finding consistent with treatment-related sarcoid-like adenopathy. **(g)** Fused PET/CT image of the chest obtained 4 months after completion of treatment shows resolution of the mediastinal nodes, a finding compatible with resolution of treatment-related sarcoid-like adenopathy.

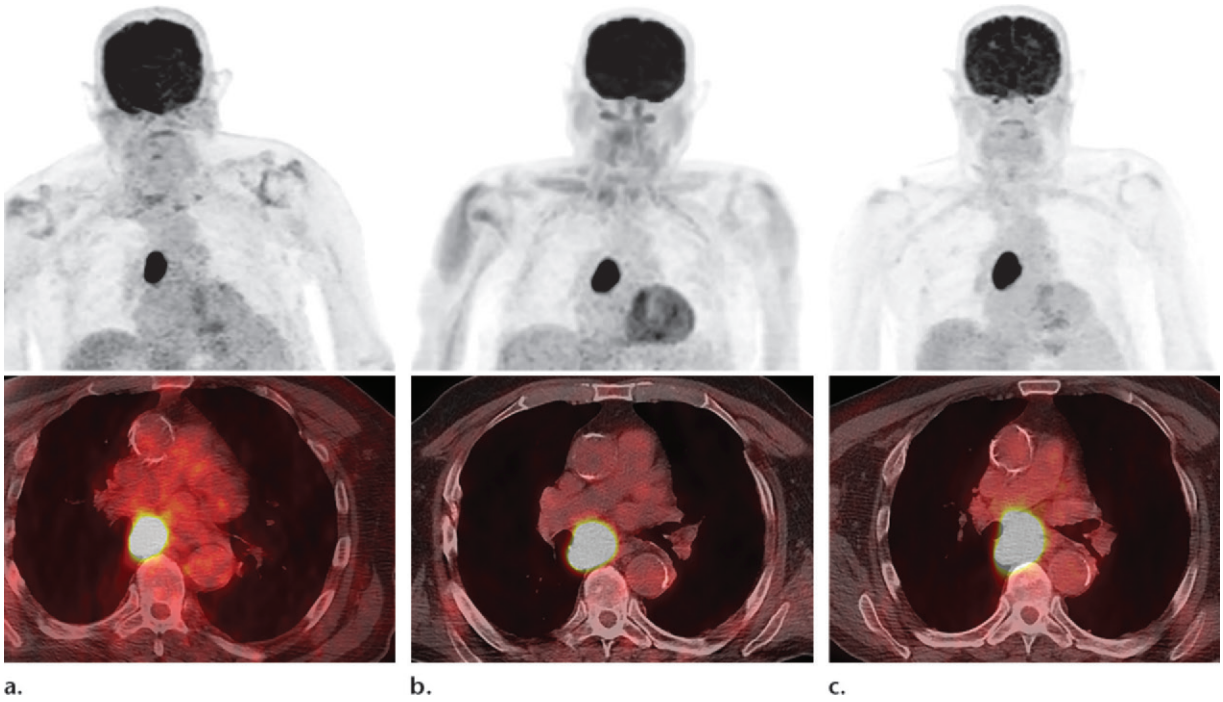


Figure 3. Stable disease. **(a)** MIP PET (top) and fused PET/CT (bottom) images of the chest obtained 2 months after completion of ipilimumab therapy show a metabolically active metastatic subcarinal lymph node. **(b)** MIP PET (top) and fused PET/CT (bottom) images of the chest obtained 4 months after completion of treatment show stability of the metastatic subcarinal node. No new FDG-avid metastatic disease is seen. **(c)** MIP PET (top) and fused PET/CT (bottom) images of the chest obtained 7 months after completion of treatment show continued stability of the metastatic subcarinal lymph node. There was a minimal increase in size that is likely treatment related but no change in FDG avidity. Furthermore, there was no evidence of new disease. Typically, progression-free survival after traditional cytotoxic chemotherapy is approximately 2–3 months in patients with metastatic melanoma. This patient demonstrated clinically significant stable metastatic disease after cancer immunotherapy.

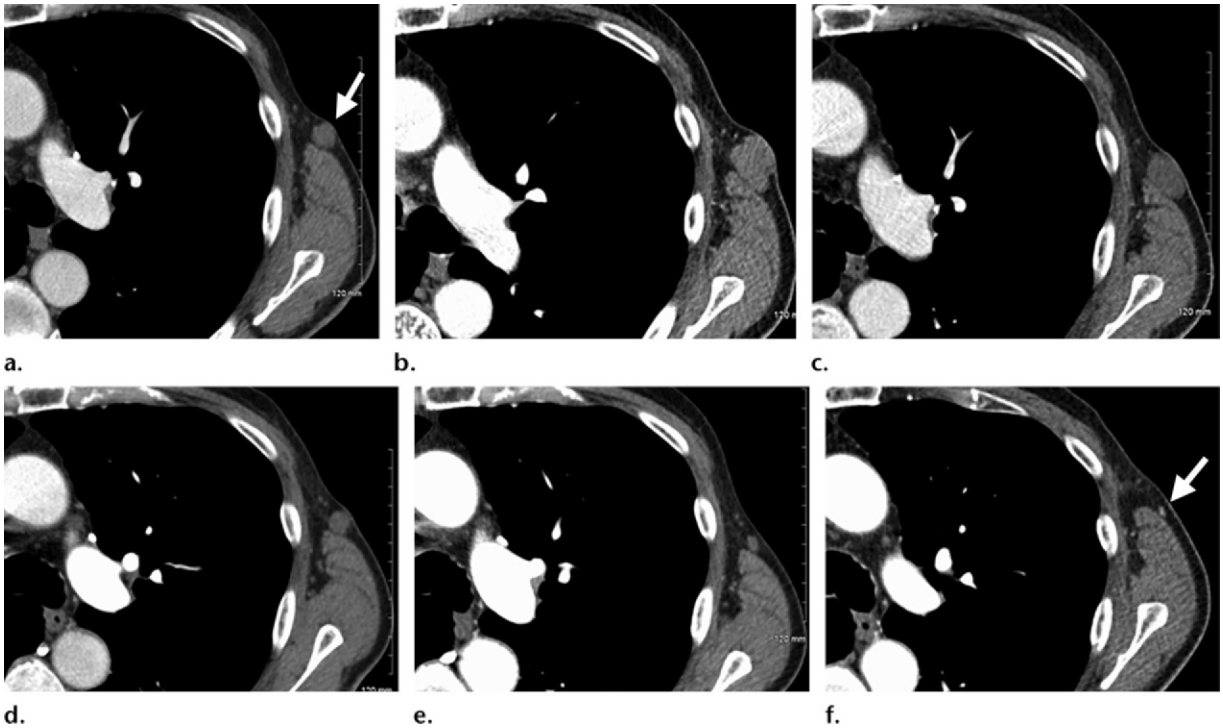


Figure 4. Tumor enlargement followed by treatment response. **(a)** Axial contrast-enhanced CT image of the chest obtained before ipilimumab therapy shows a left axillary nodal metastasis (arrow). **(b)** Axial CT image of the chest obtained 3 weeks after completion of treatment shows a marked increase in the size of the metastatic axillary lymph node. **(c)** Axial CT image obtained 4 weeks after the initial posttreatment imaging study—per the immune-related response criteria guidelines—and 7 weeks after completion of treatment shows the axillary lymph node slightly decreased in size. **(d, e)** Axial CT images obtained 7 months **(d)** and 13 months **(e)** after treatment show a continued decrease in size of the lymph node. **(f)** Follow-up CT image obtained 26 months after completion of treatment shows a 3-mm partially calcified lymph node (arrow) representing resolution of the left axillary nodal metastatic disease.

monitor tumor response to immunotherapy has also been reported (14). The feasibility of these imaging strategies in routine clinical practice is under active research.

Immune-related Adverse Events

Enhancement of the immune system to fight cancer can also result in unintended autoimmune-mediated complications. These potential treatment-related complications have been termed *immune-related adverse events*. Adverse effects of immunotherapy are either a result of the induction of autoimmunity or of a proinflammatory state (12).

As was previously discussed, recombinant cytokines have a high toxicity profile, which often limits the treatment population and the duration of treatment. Toxic effects that are associated with recombinant cytokines involve multiple organ systems, including the neurologic, gastrointestinal, renal, hepatic, cardiac, pulmonary, skin, muscular, endocrine, and hematologic systems (7). With the novel immunomodulatory CTLA-4 inhibitor, the most commonly encountered immune-related adverse events are enterocolitis (eg, diarrhea and colitis), hepatitis, dermatitis (eg, pruritis, rash, erythema, vitiligo), and endocrinopathies (15).

Immune-related adverse events can occur early, even after the first treatment, demonstrating that patients may be susceptible from the time the first dose is administered; in the case of ipilimumab, the majority of adverse events occurred during the 12-week treatment induction period (10,15). The median onset of skin-related events occurred around 3 weeks, hepatitis-related events occurred around 3–9 weeks, gastrointestinal-related events occurred around 8 weeks, and endocrinopathy-related events occurred between 7 and 20 weeks (15).

Immune-related adverse events can be successfully managed with use of published management guidelines. Management strategies include delaying a scheduled dose of immunotherapy, administering corticosteroids, and discontinuing therapy, depending on the severity of the adverse event (15). With early diagnosis, close clinical follow-up, and appropriate clinical management, immune-related adverse events can be safely managed in patients undergoing immunomodulatory therapy.

Currently, it is not known which patients are most susceptible to immune-related adverse events after immunomodulating therapy. However, an interesting correlation between development of autoimmune-mediated side effects and response to treatment has been made: An early clinical study with ipilimumab demonstrated a positive correlation between response to treatment and development of autoimmune toxic effects (10).

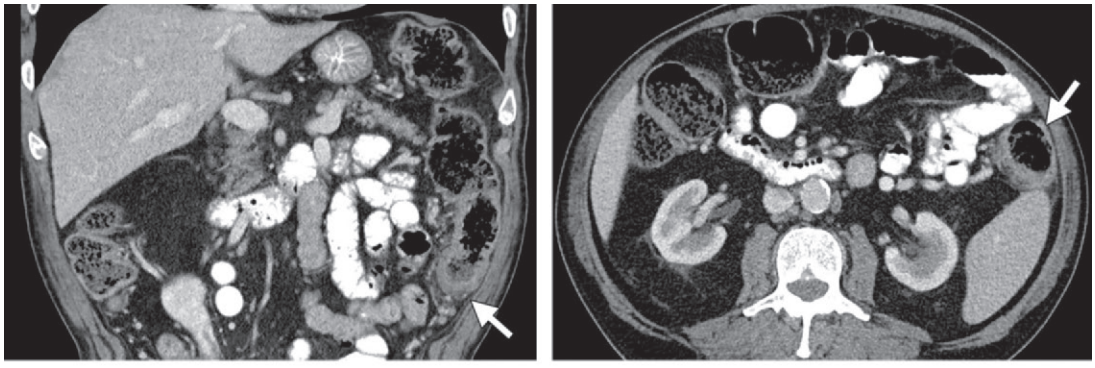
Imaging Findings of Immune-related Adverse Events

It is important for the imager to recognize the unique adverse events associated with immunotherapy to guide appropriate treatment and avoid potential imaging pitfalls that could be mistaken for metastatic progression of disease. Colitis is an important complication that requires prompt diagnosis and treatment. The highest mortality associated with immune-related adverse events occurred as a result of severe colitis, with the worst outcomes resulting from prolonged time between diagnosis and appropriate treatment of immune-related colitis (15). The recognition of colitis findings in a patient with a history of immunomodulatory cancer treatment should prompt the imager to include autoimmune colitis in the differential diagnosis. Figure 5 shows a case of autoimmune colitis after treatment with ipilimumab. The diagnosis of colitis was made at imaging, but because the possibility of autoimmune colitis was not recognized, the patient underwent antibiotic therapy instead of corticosteroid therapy, which resulted in a delayed accurate diagnosis that was complicated by colonic bowel perforation. Two patterns of autoimmune colitis associated with ipilimumab treatment were previously described: diffuse colitis, which manifests as watery diarrhea and is successfully treated with corticosteroid therapy, and segmental colitis in the setting of diverticulosis, which manifests as watery or bloody diarrhea and is treated with corticosteroid and antibiotic therapy (16).

Autoimmune hepatitis may be incidentally seen as periportal edema and hypoattenuation of the edematous liver parenchyma at CT or as periportal or portal vein hyperechogenicity at ultrasonography (17,18). These imaging findings are not specific for autoimmune hepatitis, but the imager should recognize the possibility of autoimmune hepatitis in the setting of cancer immunotherapy.

Endocrinopathies that are reported with use of ipilimumab include autoimmune hypophysitis (Fig 6) and thyroiditis (Fig 7), which can both be seen at imaging. It is important to differentiate autoimmune hypophysitis from new metastatic disease. Other less common immune-related adverse events that may be diagnosed at imaging include autoimmune pancreatitis (Fig 8), myositis, arthritis (Figs 9, 10), sarcoid-like reaction (Figs 2b, 2f, 2g, 11), lymphocytic vasculitis, organizing pneumonia, and fasciitis (19–21). Sarcoid-like adenopathy and pancreatitis are important immune-related adverse events that should be recognized and differentiated from metastatic

Figure 5. Autoimmune colitis in a patient with metastatic melanoma who presented to the emergency department with abdominal pain approximately 1 month after receiving the third dose of ipilimumab therapy. **(a, b)** Coronal reformatted **(a)** and axial **(b)** CT images of the abdomen show wall thickening of a segment of the descending colon (arrow) with associated inflammatory stranding in the pericolonic fat, a finding compatible with colitis. A diagnosis of diverticulitis was made, and the patient underwent antibiotic therapy. Unfortunately, the patient did not improve and presented a few weeks later with rectal bleeding resulting from colonic perforation. A diagnosis of autoimmune colitis was then made, and corticosteroid therapy was begun. **(c)** MIP PET (left), fused axial PET/CT (top right), and localization CT (bottom right) images of the abdomen from a FDG PET/CT study performed 1 month after initiation of corticosteroid therapy show persistent descending colonic wall thickening with intense inflammatory FDG uptake and surrounding inflammatory pericolonic fat stranding. Infliximab therapy was begun. **(d)** Follow-up PET/CT image (top right) shows near-complete resolution of the colitis; MIP PET image (left) shows FDG uptake in the left lower abdomen, a finding that corresponds to physiologic bowel activity near the colostomy site; and localization CT image (bottom right) shows a marked decrease in colonic wall thickening and pericolonic fat stranding.



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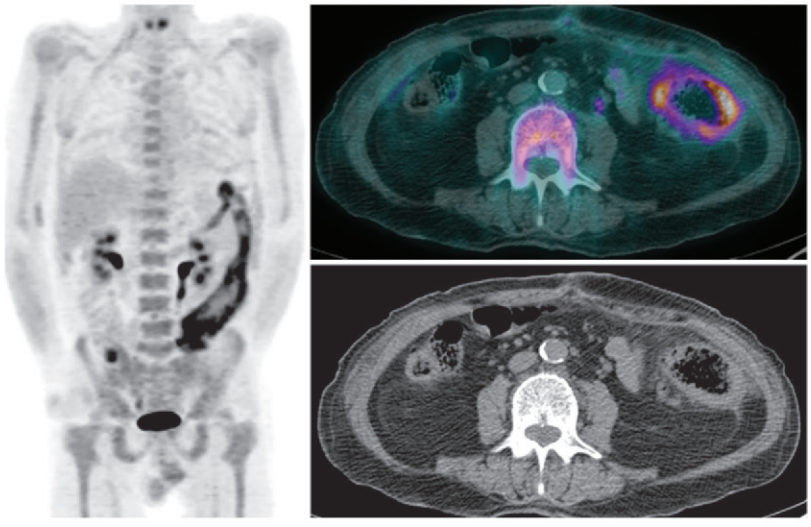

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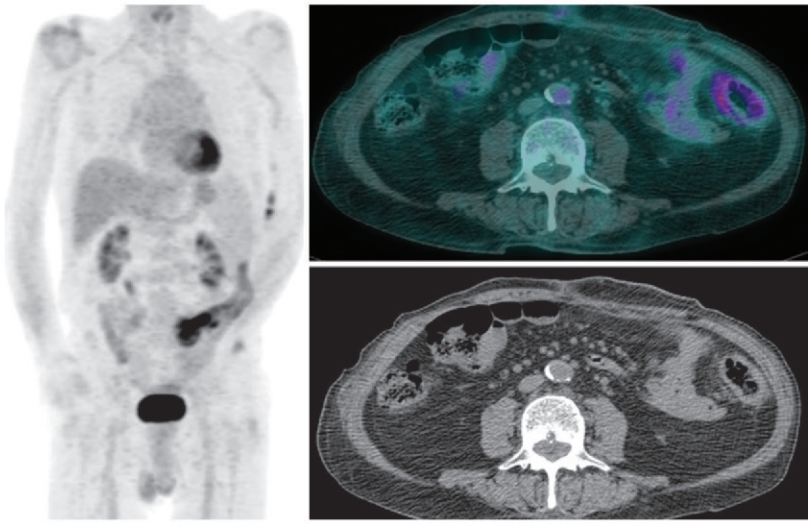

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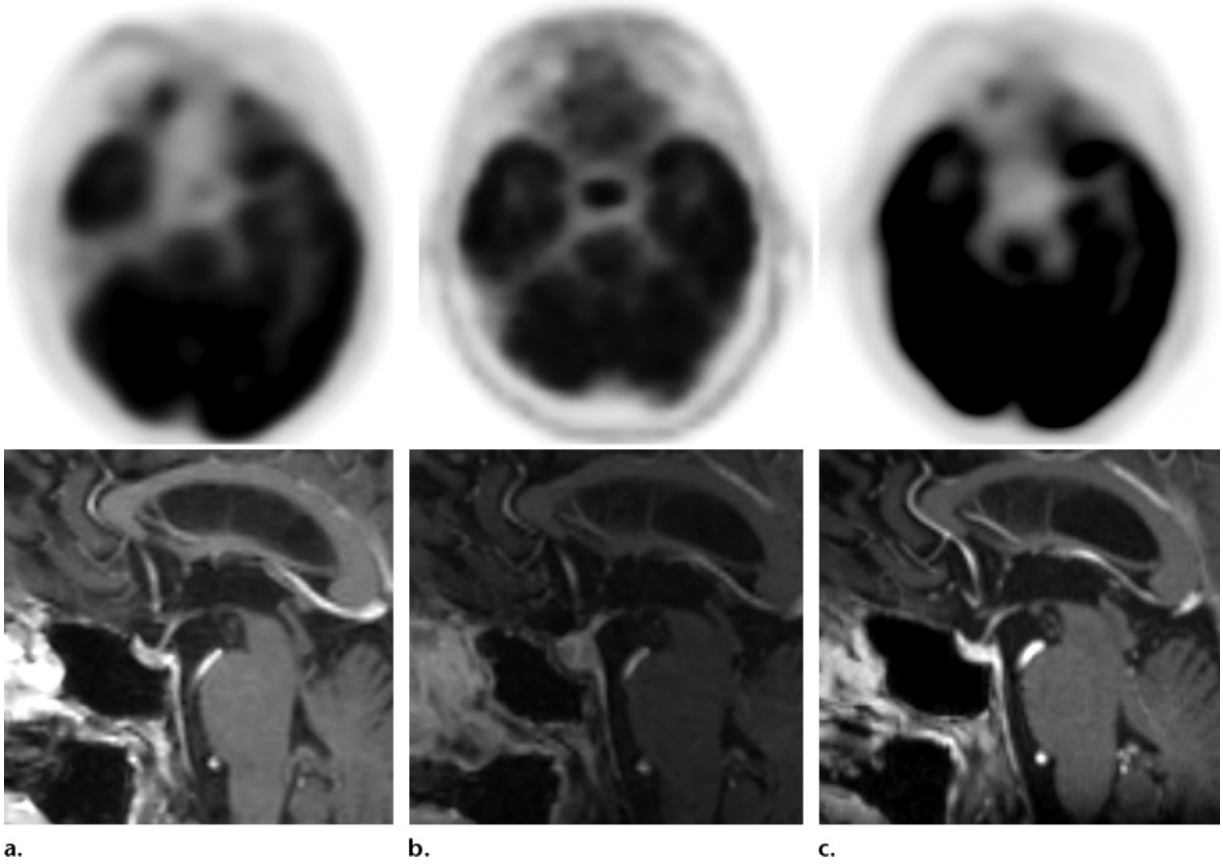
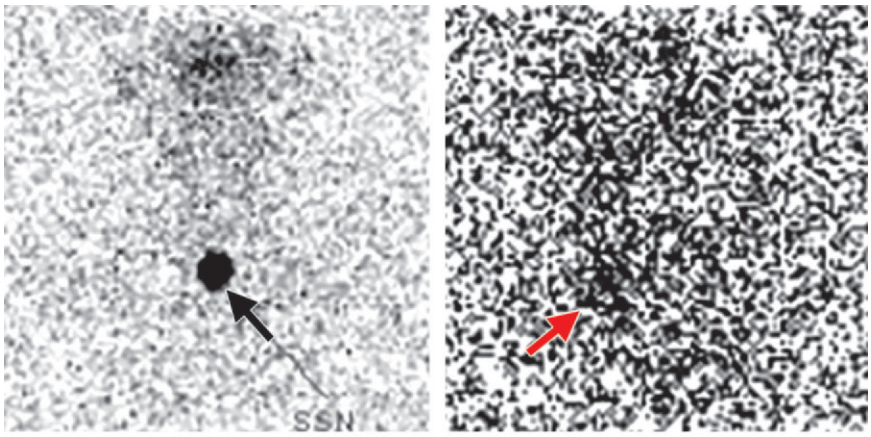


a. b. c.

Figure 6. Autoimmune hypophysitis in a patient with metastatic melanoma. **(a)** Top: Axial PET image of the brain obtained before ipilimumab therapy at the level of the pituitary sella shows very mild physiologic FDG uptake in the sella. Bottom: Sagittal midline contrast-enhanced MR image of the brain shows the pituitary gland and infundibulum, which appear normal. One month after completion of ipilimumab therapy, the patient presented with fatigue. Results of endocrine laboratory tests indicated central hypothyroidism (low thyroid-stimulating hormone, T4, and T3), low cortisol, and low testosterone levels. **(b)** Axial PET image of the brain obtained at the level of the sella (top) shows new abnormally increased FDG uptake in the sella, a finding that corresponds to an enlarged pituitary gland and infundibulum at sagittal MR imaging (bottom). **(c)** Follow-up PET (top) and MR (bottom) images obtained 1 month after a diagnosis of hypophysitis and 2 months after completion of corticosteroid therapy show resolution of abnormal FDG uptake in the sella and a normal appearance of the pituitary gland and infundibulum. Immune-mediated hypophysitis should not be mistaken for new metastatic disease after immunomodulating cancer therapy.



a. b.

Figure 7. Autoimmune thyroiditis in a patient with metastatic melanoma, clinical symptoms of thyrotoxicosis, and a low thyroid-stimulating hormone level approximately 6 weeks after completion of ipilimumab therapy. **(a)** Anterior planar image of the neck and upper chest from iodine-123 (^{123}I) thyroid scintigraphy shows no radionuclide uptake in the thyroid gland with faint physiologic radioiodine activity in the oropharynx. The sternal notch marker (arrow) denotes the inferior midline of the neck. **(b)** Anterior pinhole image of the neck shows faint radioiodine uptake in the right aspect of the thyroid gland (arrow). This imaging pattern at ^{123}I radioiodine scintigraphy is most consistent with thyroiditis.

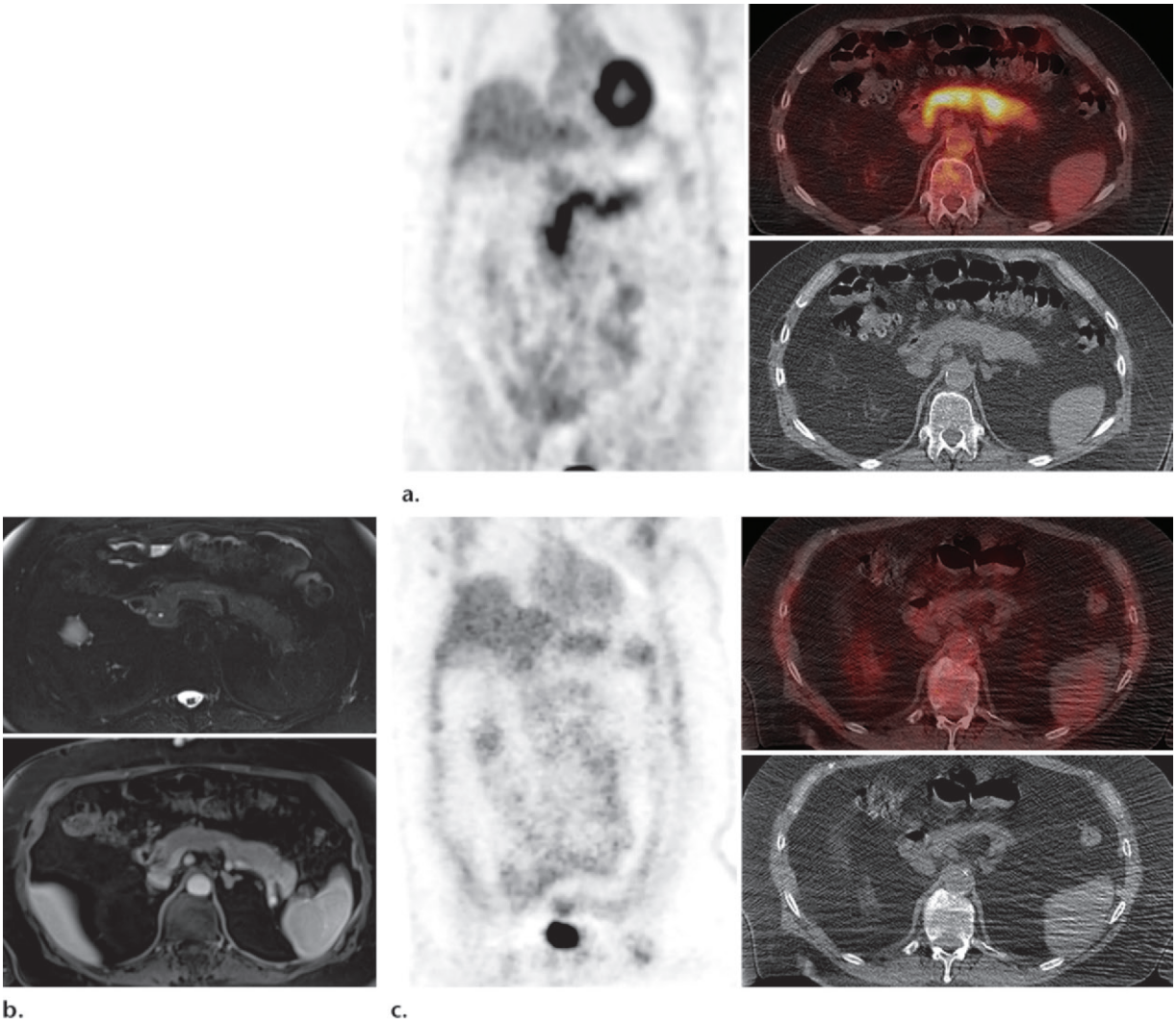


Figure 8. Autoimmune pancreatitis in a patient who was asymptomatic and presented for follow-up imaging 3 months after completion of ipilimumab therapy. **(a)** MIP PET (left) and fused axial PET/CT (top right) images show intense FDG uptake in the pancreas. Localization CT image obtained at the level of the pancreas (bottom right) shows a mildly enlarged pancreas with no peripancreatic inflammatory changes and rounded pancreatic contours that can be described as having the "sausage" appearance of autoimmune pancreatitis. **(b)** Follow-up T2-weighted fat-saturated (top) and contrast-enhanced T1-weighted fat-saturated (bottom) MR images obtained at the level of the pancreas to evaluate for pancreatic metastases show no focal pancreatic lesions suspicious for metastatic disease. **(c)** Follow-up MIP PET image (left) obtained 1 month later shows no abnormal FDG uptake in the pancreas. PET/CT image (top right) shows resolution of FDG uptake in the pancreas. Localization CT image of the pancreas (bottom right) shows interval decrease in the size of the pancreas.

disease. In addition, myocarditis, pericarditis, temporal arteritis, conjunctivitis, and pneumonitis are rare adverse events that currently have no published imaging case reports but could potentially be diagnosed at imaging.

Future Directions

New T-cell immunomodulating therapies are already being investigated in the clinical setting. Programmed death 1 protein (PD-1) is another T-cell surface immune checkpoint molecule with a similar structure to that of CTLA-4 (6). Two known ligands of PD-1 (programmed death receptor ligand 1 [PD-L1] and programmed death receptor ligand 2 [PD-L2]) have been identified. Many tumors, including melanoma, ovarian cancer, renal cancer, hepatocellular carcinoma, and glioblastoma, have been found to express PD-L1. Multicenter clinical trials that use anti–PD-L1 antibody for treatment of non–small cell lung cancer, melanoma, and colorectal, renal cell, ovarian, breast, pancreatic, and gastric cancers are under way (2,22).

Whereas CTLA-4 is involved in the early initial activation of T-cells in the lymphatic tissues, PD-1 is involved in the later phase of activation, which affects T-cells in the peripheral tissues that have already undergone initial activation (2,3,6). This PD-1 function that occurs during the later phase of T-cell activation is thought to be the

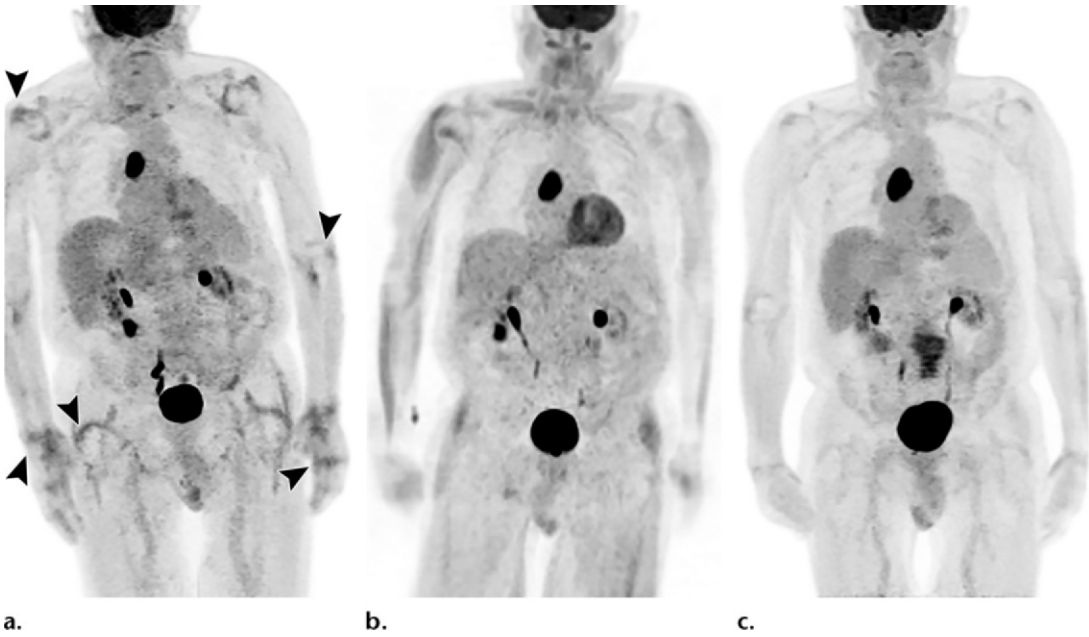


Figure 9. Arthritis in the same patient as in Figure 3. **(a)** MIP PET image obtained 2 months after completion of ipilimumab therapy shows diffuse periarticular FDG uptake (arrowheads) in the joints of the shoulders, elbow, wrists, hands, and hips. **(b, c)** Follow-up MIP PET images obtained 4 months **(b)** and 7 months **(c)** after completion of therapy show resolution of diffuse periarticular FDG uptake and very mild physiologic periarticular activity. FDG activity projecting over the mid abdomen **(c)** corresponds to physiologic bowel activity. The patient was asymptomatic and did not require corticosteroid therapy for transient arthritis.

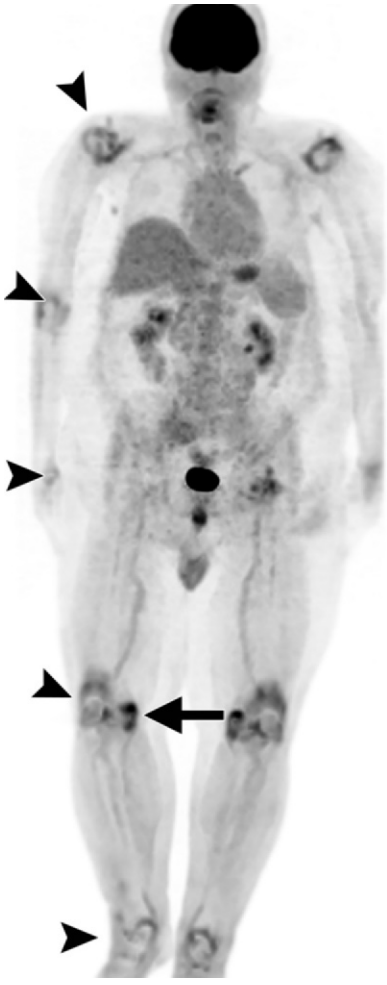


Figure 10. Immune-mediated arthritis in a patient with metastatic melanoma who underwent ipilimumab therapy. MIP PET image shows a diffuse pattern of periarticular FDG uptake (arrowheads) compatible with immune-mediated arthritis and evidence of superimposed degenerative osteoarthritis in the medial compartments of the bilateral knees (arrow).

reason why fewer autoimmune-mediated toxic effects are associated with anti–PD-1/PD-L1 antibodies than with anti–CTLA-4 antibodies such as ipilimumab (22).

Conclusions

Oncologic imaging plays an integral role in the care of patients with cancer. As a result, it is crucial that radiologists keep abreast of the major advancements in treatment of cancer. Advancements in cancer immunotherapy challenge the current imaging approach to evaluation of cancer treatment response and treatment-related complications. Radiologists must recognize the novel treatment response patterns and the wide range of autoimmune-related toxici effects that should not be mistaken for disease progression. In addition, early recognition of potential immune-related adverse events and recommendations for appropriate clinical management by the cognizant radiologist may be critical to successful management of immune-related toxic effects.

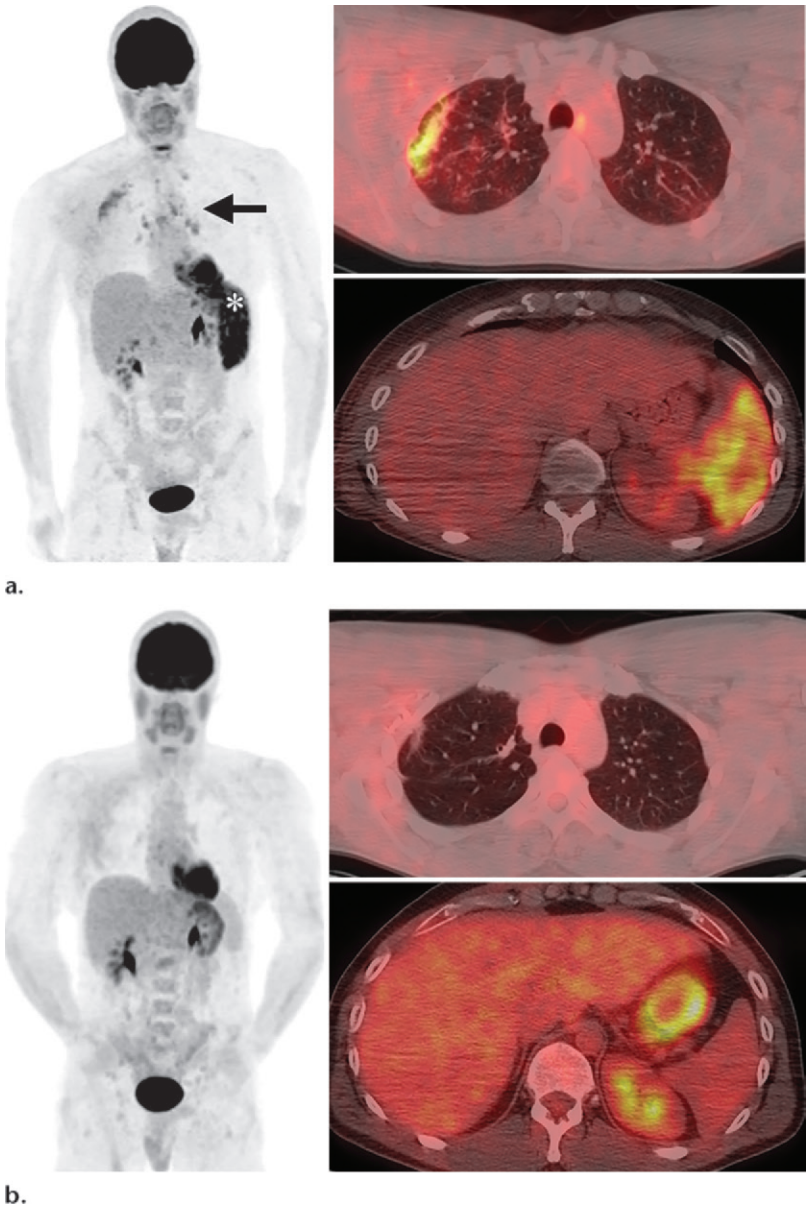


Figure 11. Immune-related sarcoid-like reaction in a patient with oligometastatic melanoma to a right axillary lymph node after undergoing radiation therapy to the right axilla and recombinant cytokine therapy with interferon-α. **(a)** Left: MIP PET image obtained 2 months after treatment shows FDG uptake in the paratracheal mediastinal and bilateral hilar nodes in the chest (arrow), as well as in the spleen (*). Top right: Fused axial PET/CT image of the lung apices shows inflammatory FDG uptake within radiation pneumonitis changes of the right lung apex. Bottom right: Fused PET/CT image of the upper abdomen shows multifocal areas of intense FDG uptake in the spleen. **(b)** Corresponding images obtained 5 months after treatment show complete resolution of FDG uptake in the mediastinal and hilar nodes, and spleen. In addition, the right apical radiation pneumonitis has resolved. Physiologic FDG uptake is seen in the fundal wall of the stomach on the MIP PET (left) and fused axial PET/CT (right) images.

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