Radiologic Aspects of Immune-Related Tumor Response Criteria and Patterns of Immune-Related Adverse Events in Patients Undergoing Ipilimumab Therapy

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OBJECTIVE. The objective of this article is to illustrate examples of radiologic immune-related response criteria and toxicity in patients with advanced melanoma treated with the immunotherapeutic agent ipilimumab.

CONCLUSION. Novel immune-related tumor response criteria should be applied to patients undergoing therapy with ipilimumab for advanced melanoma. Ipilimumab also produces a spectrum of immune-related adverse effects that can be recognized radiologically.

Keywords: adverse drug effects, immune response criteria, ipilimumab, melanoma, oncologic imaging, therapy

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Ipilimumab is a recently U.S. Food and Drug Administration (FDA)-approved novel immunotherapeutic drug that has shown promise in the treatment of advanced melanoma. Systemic therapy for advanced melanoma prior to ipilimumab has had limited success to date with only two agents approved by the FDA: dacarbazine and interleukin 2. Until recently, no randomized controlled studies have shown a survival benefit with any agent in patients with stage IV melanoma. Early clinical studies have shown that ipilimumab as monotherapy or in combination with other agents can induce durable responses or stabilization of disease in a significant proportion of patients with advanced melanoma [1]. A recent large multicenter phase III trial showed a survival benefit in patients treated with ipilimumab [2]. As a result, ipilimumab was approved by the FDA in March 2011.

Ipilimumab works by augmenting the body's immune response to cancer cells. Cytotoxic T lymphocyte antigen–4 (CTLA4) is an immune checkpoint molecule that downregulates T-cell activation [2]. Ipilimumab is a fully humanized monoclonal antibody that blocks CTLA4 and thereby augments the T-cell immune response to cancer cells [2]. The purpose of this article is to illustrate the unique patterns of radiologic response and toxicity related to ipilimumab therapy. The imaging examples used are from patients treated on an institutional review board–approved, expanded-access trial at a tertiary referral oncology center. The study included 62 patients and illustrated several important aspects of immunotherapy.

Measurement of Tumor Response With Immunotherapy

The first response criteria for solid tumors were developed approximately 30 years ago by the World Health Organization (WHO) [3]. More recently, these criteria have been superseded by the Response Evaluation Criteria in Solid Tumors (RECIST) published in 2000 [4] and updated in 2009 (RECIST 1.1) [5]. Using the latter criteria, early increases in tumor size or the appearance of new lesions is classified as "progressive disease," a term now synonymous with treatment failure. However, the unique method of action of immune-potentiating agents such as ipilimumab has led to the formulation of novel radiologic tumor response criteria (i.e., immune-related response criteria) [6]. These new criteria are needed because early treatment effects of these agents can result in an initial increase in the size of a tumor followed by a reduction in tumor size. In addition, tumor response can be seen in spite of the presence of new lesions. Therefore, it is important that radiologists working in an oncology setting recognize the unique patterns of response and apply the appropriate response criteria.

Immune-related response criteria were proposed by a collaborative group of approximately 200 oncologists, immunotherapists, and regulatory experts who convened in 2004 and 2005 to devise these criteria on the basis of clinical observations [6]. These criteria

were validated using a series of large multinational studies including 487 patients treated with ipilimumab. This group has advocated their use in clinical trials of immunotherapeutic agents to allow more comprehensive evaluation of tumor response [6].

Patterns of Tumor Response to Ipilimumab

Response to treatment with ipilimumab can be complete (immune-related complete response) or partial (immune-related partial response). Four distinct patterns of tumor response to ipilimumab have been described [6, 7]: type A, reduction in size of baseline lesions with no new lesions; type B, stable disease with no significant change in the size of the baseline lesions that may or may not be followed by a slow, steady decline in tumor size; type C, initial increase in tumor burden followed by response; and type D, reduction in total tumor burden in spite of the appearance of new lesions.

Examples of each pattern of tumor response are illustrated in Figures 1–6. In a recent article, Wolchok et al. [6] reported that all of the patterns of response mentioned (i.e., types A, B, C, and D) were associated with favorable survival.

The immune-related tumor response criteria are derived from the WHO tumor response criteria using the sum of the products of the two largest perpendicular diameters of the index lesions to determine total tumor burden and the same thresholds to determine tumor response and progression [6]. However, a novel concept introduced in the immune-related tumor response criteria is that new, measurable lesions are added to the total tumor burden as they appear and are reassessed on subsequent studies; these new lesions would have automatically signaled disease progression using the WHO criteria. When new lesions are present on a postbaseline restaging assessment, patients are not considered to have progressive disease (immune-related progressive disease) if the total tumor burden has not increased by more than 25%. The first posttreatment scan should be obtained at 12 weeks, followed by subsequent scans every 8 weeks. However, in patients who have progressive disease (immune-related progressive disease) on imaging, this finding must be confirmed with a second scan at least 4 weeks later so that a type C response pattern may be identified [6].

A range of autoimmune effects or "immune-related adverse events" have been described in patients undergoing treatment with ipilimumab: enterocolitis, hypophysitis, hepatitis, dermatitis, myopathy, pancreatitis, and nephritis [8–11]. A sarcoidosislike reaction has also been reported [12].

The presence of immune-related adverse events has been shown to be predictive of better clinical responses and outcomes [8]. However, these effects can be quite severe and can result in cessation of treatment. Several of these immune-related adverse events may be asymptomatic early in their clinical course and may be detected only during follow-up imaging studies such as CT, MRI, or PET/CT. Therefore, specific patterns of immune-related adverse events that are detectable radiologically should be recognized early and communicated to the clinician.

The most commonly reported major toxicity is grade 3 or 4 autoimmune enterocolitis, occurring in approximately 10–20% of patients [2, 13]. The imaging features of ipilimumab-induced colitis have not been previously described to date, but in our experience the CT appearance of ipilimumab-induced colitis mimics that of inflammatory bowel disease with diffuse or focal colonic wall thickening, pericolonic inflammatory changes (fat stranding, mesenteric hypervascularity [comb sign], and free fluid), and occasionally intestinal perforation. Figures 7 and 8 show the CT features of colitis in patients treated with ipilimumab. Colitis may be severe enough to require systemic corticosteroids or anti–tumor necrosis factor agents such as infliximab, although the incidence of life-threatening perforation is rare (4 in 700) [8, 14].

Autoimmune hypophysitis in patients treated with ipilimumab occurs in approximately 5% of cases [8]. Presenting symptoms include headache, visual field defect, and signs of hypopituitarism [8]. On MRI, enlargement of the pituitary gland is seen in most cases, often with suprasellar extension [15] (Fig. 9). MRI findings may precede the development of clinical symptoms in some cases [15].

Ipilimumab-induced hepatitis is rare, occurring in fewer than 5% of cases, and usually presents as an asymptomatic rise in liver function test values [8]. This change in laboratory values is usually reversible on discontinuation of therapy, but courses of systemic corticosteroids or infliximab may be indicated in severe cases [8]. The imaging features of hepatitis, when present, are often nonspecific, but signs include steatosis, hepatomegaly, and periportal edema (Fig. 10).

Conclusion

Ipilimumab is a recently FDA-approved immunotherapeutic new agent for the management of patients with advanced melanoma and works by augmenting the body's immune response to tumor cells. Novel immune-related tumor response criteria have been recently described and should be applied to patients undergoing therapy with ipilimumab for advanced melanoma. Ipilimumab also produces a spectrum of immune-related adverse effects that can be recognized radiologically.

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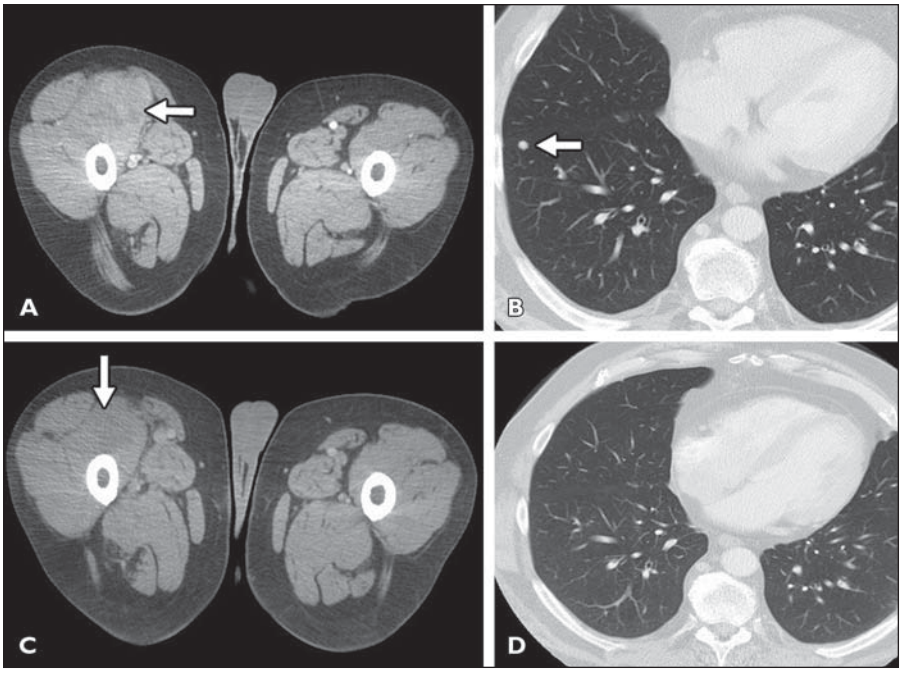

Fig. 1—Type A response to ipilimumab therapy in 55-year-old man with metastatic melanoma to right thigh and lung.
A and **B,** Baseline CT images obtained before treatment show large mass in anterior compartment of right thigh (*arrow*, **A**) and right lower lobe pulmonary nodule (*arrow*, **B**).
C and **D,** CT images obtained 12 weeks after commencing treatment with ipilimumab show significant reduction in size of right thigh mass (*arrow*, **C**) and interval resolution of right lung nodule.

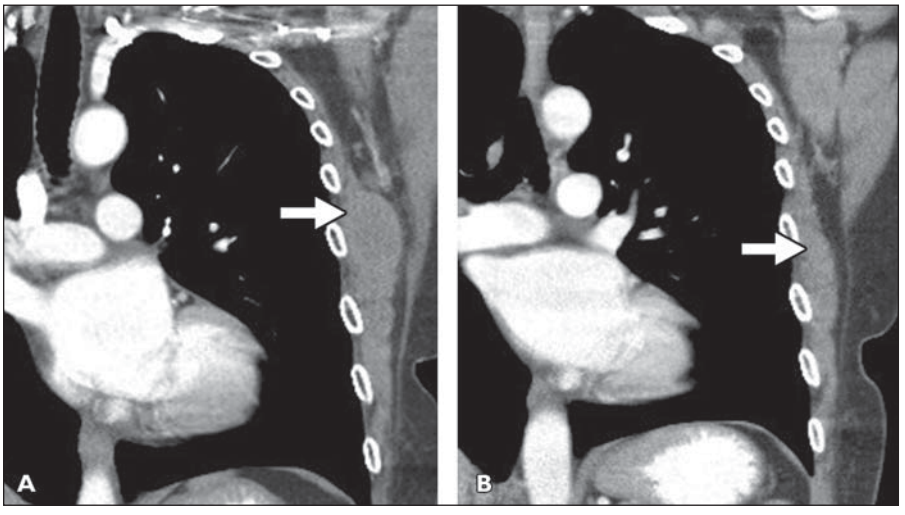

Fig. 2—Type A response to ipilimumab therapy in 60-year-old woman with metastatic melanoma to left chest wall.
A, Baseline coronal reformatted CT image obtained before treatment shows soft-tissue mass (*arrow*) in left axilla and chest wall abutting ribs.
B, Repeat CT image obtained 12 weeks after commencing ipilimumab therapy shows significant response to treatment (*arrow*).

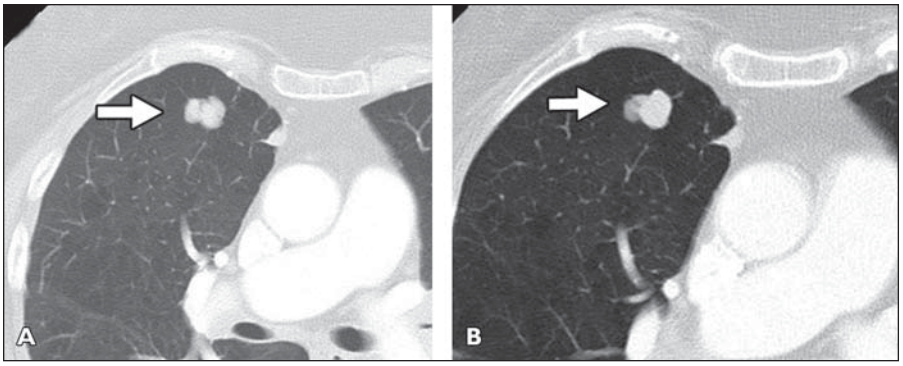

Fig. 3—Type B response to ipilimumab therapy in 71-year-old woman with metastatic melanoma to lung.
A, Baseline CT image obtained before treatment shows lobulated nodule (*arrow*) in right middle lobe.
B, Repeat CT image obtained 12 weeks after commencing ipilimumab therapy shows no significant change in size of nodule (*arrow*), indicating stable disease.

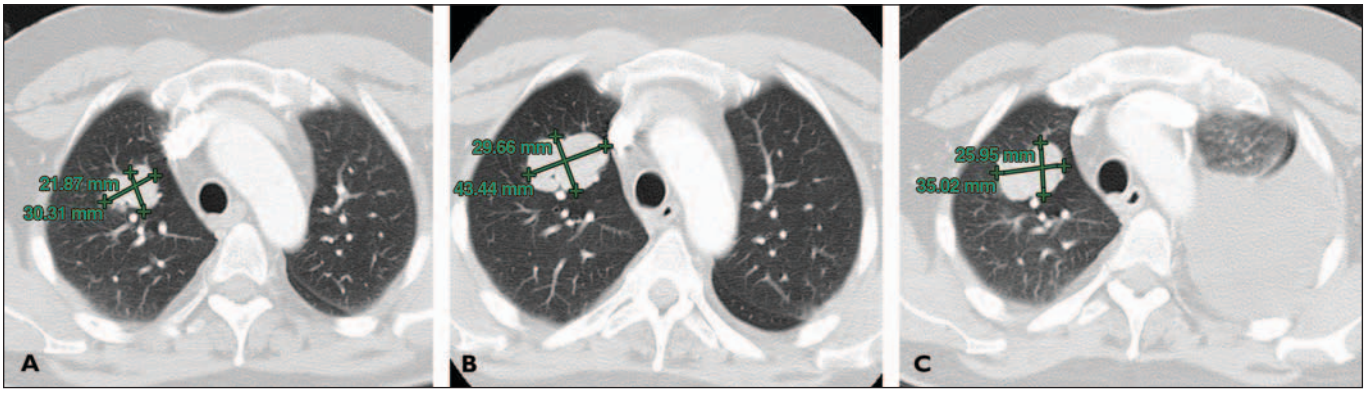

Fig. 4—Type C response to ipilimumab therapy in 46-year-old man with metastatic melanoma to right lung.
A, Baseline CT image obtained before treatment shows mass in right upper lobe.
B, Repeat CT image obtained 8 weeks after commencing ipilimumab therapy shows significant increase in size of mass.
C, CT image obtained 12 weeks after commencing therapy shows interval decrease in size of mass, almost to baseline level. Note also interval development of left pleural effusion.

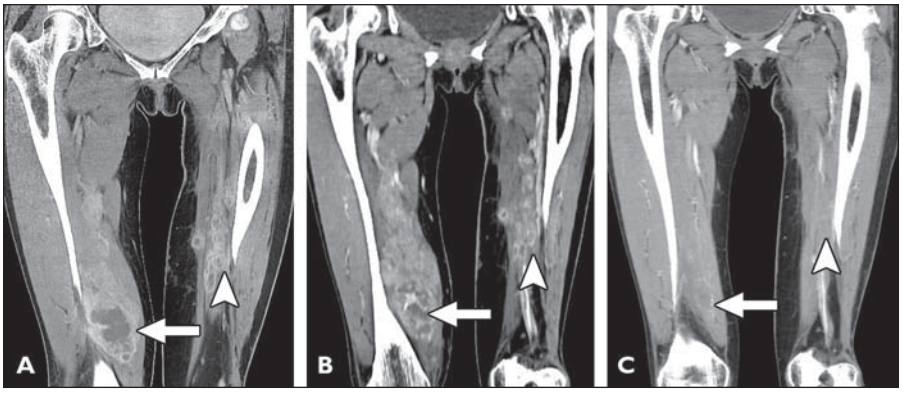

Fig. 5—Type C response to ipilimumab therapy in 56-year-old woman with metastatic melanoma to both lower extremities.
A, Lower extremity coronal reformatted CT image shows multiple bilateral masses in medial compartments of both thighs (*arrow* and *arrowhead*).
B, Repeat CT image obtained 12 weeks after commencing ipilimumab therapy shows interval enlargement of masses (*arrow* and *arrowhead*).
C, Repeat CT image at 24 weeks shows significant response. Arrow and arrowhead point to areas where masses shown in **A** and **B** were.

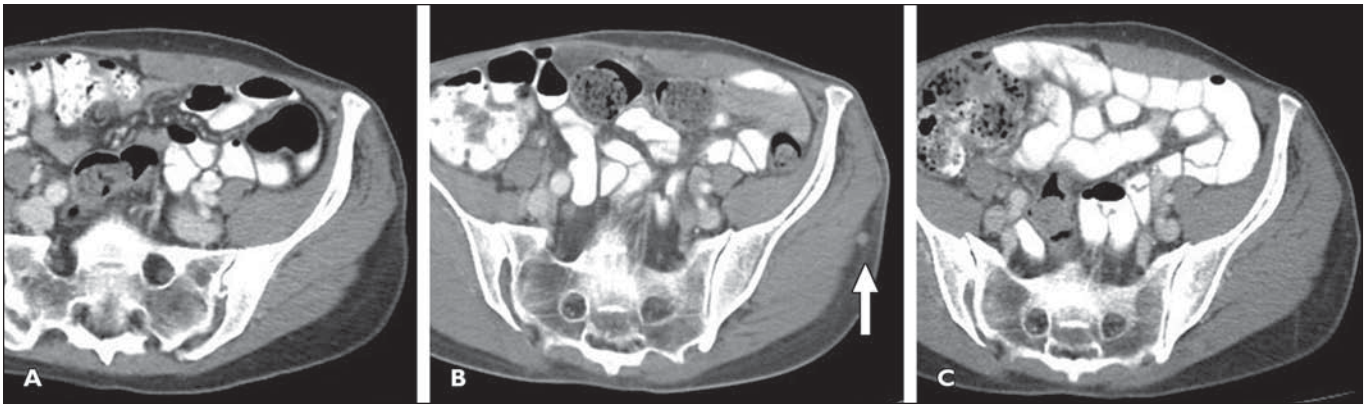

Fig. 6—Type D response to ipilimumab therapy in 56-year-old woman with metastatic melanoma.
A and **B,** CT images obtained at baseline (**A**) and 12 weeks after commencing ipilimumab therapy (**B**) show new subcutaneous nodule in left gluteal region (*arrow*, **B**), considered suspicious for new melanoma deposit; other new subcutaneous nodules were also seen.
C, Repeat CT image obtained at 24 weeks shows complete resolution of nodule. Other target lesions in same patient also showed response to treatment.

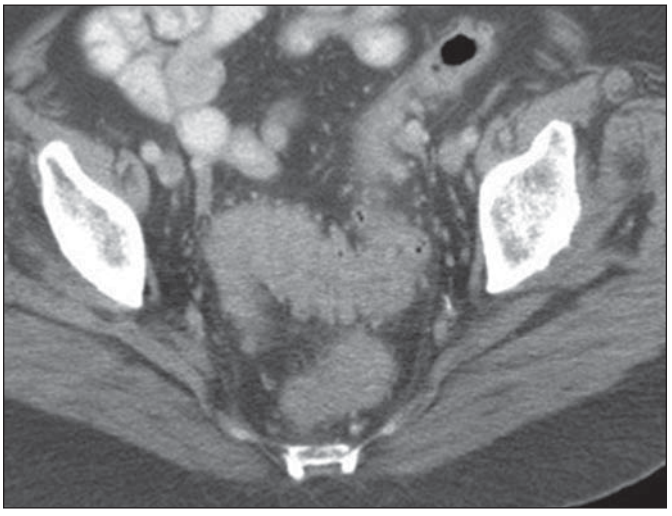

Fig. 7—71-year-old woman receiving ipilimumab for treatment of metastatic melanoma. Axial CT image of pelvis shows mural thickening of sigmoid colon with adjacent fat stranding and mesenteric hypervascularity. Colonic biopsy revealed moderate-to-severe active inflammation, consistent with ipilimumab-induced colitis.

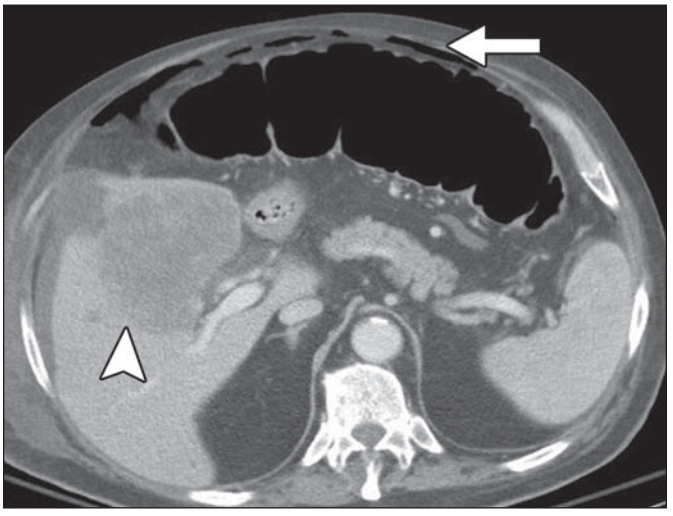

Fig. 8—73-year-old man receiving ipilimumab for treatment of metastatic melanoma. Axial CT image of abdomen shows transverse colon (*arrow*) is grossly dilated with free intraperitoneal air, indicating intestinal perforation. Note also large metastasis (*arrowhead*) in right lobe of liver. Patient underwent colectomy, and pathology revealed severe active inflammation consistent with ipilimumab-induced colitis.

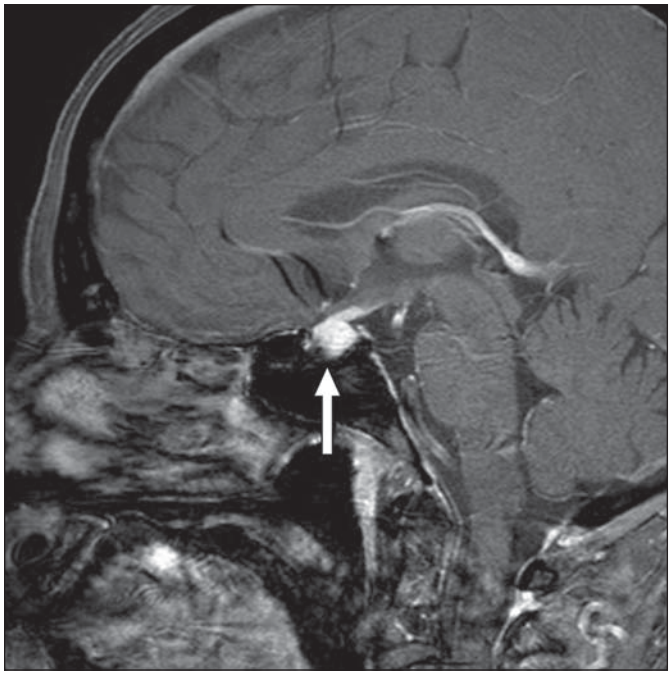

Fig. 9—71-year-old man receiving ipilimumab for treatment of metastatic melanoma who presented with new-onset headache. Sagittal T1-weighted contrast-enhanced brain MR image shows mild enlargement of pituitary gland (*arrow*) with convex superior margin, suprasellar extension, and diffuse enhancement of pituitary gland. Endocrinologic assessment confirmed hypopituitarism consistent with ipilimumab-induced hypophysitis.

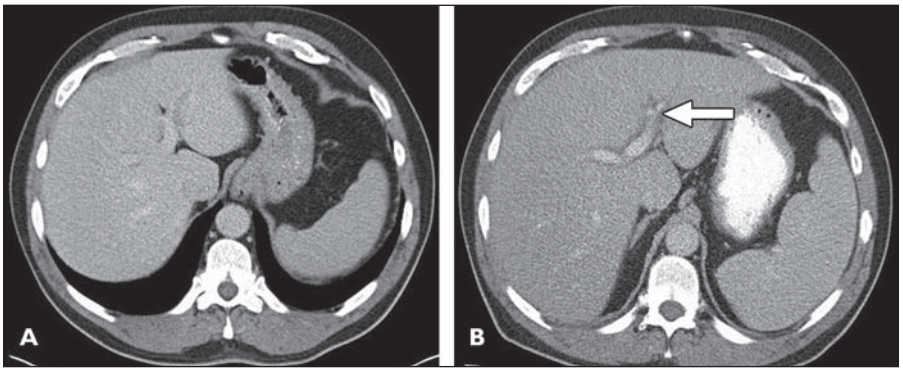

Fig. 10—59-year-old man with metastatic melanoma undergoing treatment with ipilimumab.
A, Baseline CT image obtained before treatment shows normal appearance of liver.
B, Repeat CT image obtained 8 weeks after commencing treatment because of elevated liver function test levels shows diffusely decreased attenuation of hepatic parenchyma and new periportal edema (*arrow*). Liver biopsy showed severe active hepatitis consistent with drug-induced cause.