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UNSPECIFIED

PICTORIAL ESSAY

High-dose interleukin-2 therapy related adverse events and implications on imaging

Neal R. Shah
Brandon Declouette
Kianoush Ansari-Gilani
Mohammad S. Alhomoud
Christopher Hoimes
Nikhil H. Ramaiya
Ezgi Güler

ABSTRACT

High-dose interleukin-2 (HDIL-2) therapy was initially approved by the U.S. Food and Drug Administration for metastatic renal cell carcinoma (mRCC) and metastatic melanoma. IL-2 is able to promote CD8+ T cell and natural killer (NK) cell cytotoxicity to increase tumoricidal activity of the innate immune system. HDIL-2 therapy is associated with a wide spectrum of immune-related adverse events (irAEs) that can be radiologically identified. HDIL-2 toxicity can manifest in multiple organ systems, most significantly leading to cardiovascular, abdominal, endocrine, and neurological adverse events. The collective impact of the irAEs and the rise of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors led to the demise of HDIL-2 as a primary therapy for mRCC and metastatic melanoma. However, with innovation in ICIs and the creation of mutant IL-2 conjugates, there has been a drive for combination therapy. Knowledge of the HDIL-2 therapy and HDIL-2 related adverse events with radiology relevance is critical in diagnostic image interpretation.

High-dose interleukin-2 (HDIL-2) was initially approved for the treatment of metastatic renal cell carcinoma (mRCC) and metastatic melanoma in 1992 and 1998, respectively. IL-2 was discovered as a cytokine, known as T cell growth factor. The majority of IL-2 is produced by CD4+ T cells, CD8+ T cells, natural killer (NK) cells, and activated dendritic cells. IL-2 has numerous functions which include differentiation of CD4+ T cells, promoting CD8+ T cell cytotoxicity, and promoting NK cell cytotoxicity (1). When given intravenously at high doses, IL-2 therapy gained success in a subset of patients with metastatic melanoma or mRCC who achieved complete and durable responses (1). However, the high toxicity profile of HDIL-2 restricted this therapy to a minority of patients in highly specialized centers.

Currently HDIL-2 has been relegated to a limited role in systemic therapy of mRCC and metastatic melanoma patients. Based on National Comprehensive Cancer Network (NCCN) guidelines, HDIL-2 has been useful for patients with favorable, intermediate, and poor risk clear cell mRCC patients who have excellent performance and normal organ function (2). Additionally, HDIL-2 is recommended as a second line regimen for metastatic or unresectable melanoma. HDIL-2 is contraindicated in patients with inadequate organ reserve, poor performance status, or with untreated/active brain metastases (3).

Although HDIL-2 was more commonly used in 1990s, with the innovation in immune checkpoint inhibitors (ICIs), there has been a reemergence of HDIL-2 treatment as a combination therapy. The leading theory with including ICIs is the fact that these agents work downstream during the effector phase in a tumor. With IL-2 secretion activating tumor-specific T cells, HDIL-2 therapy could potentially work synergistically with ICIs (4). One study found that there was durable antitumor activity in metastatic melanoma and mRCC patients with HDIL-2 therapy after the patient had received programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor compared to patients who had just received IL-2. Thus, HDIL-2 remains an option for patients who have progressed on ICIs (5). With additional data, combination therapy may be the new norm for metastatic melanoma and mRCC treatment.

New innovations to make HDIL-2 therapy safer has also surfaced with the creation of IL-2 conjugated with 6 releasable polyethylene glycol (PEG) chains (4). The mechanism behind PEGylated IL-2 revolves around the idea that the drug selectively binds to the IL-2R$\alpha\beta\gamma$ isoform which preferentially activates effector T cells, which limits the side effect profile. Unfortu-

From the Departments of Radiology (N.R.S., B.D., K.A.G., N.H.R., E.G.) and Hematology and Oncology (M.S.A., C.H.), University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA; Department of Medical Oncology (C.H.), Duke University School of Medicine, Durham, North Carolina, USA; Department of Radiology (E.G. ✉ *gulerezgi@yahoo.com*), Ege University Faculty of Medicine, Izmir, Turkey.

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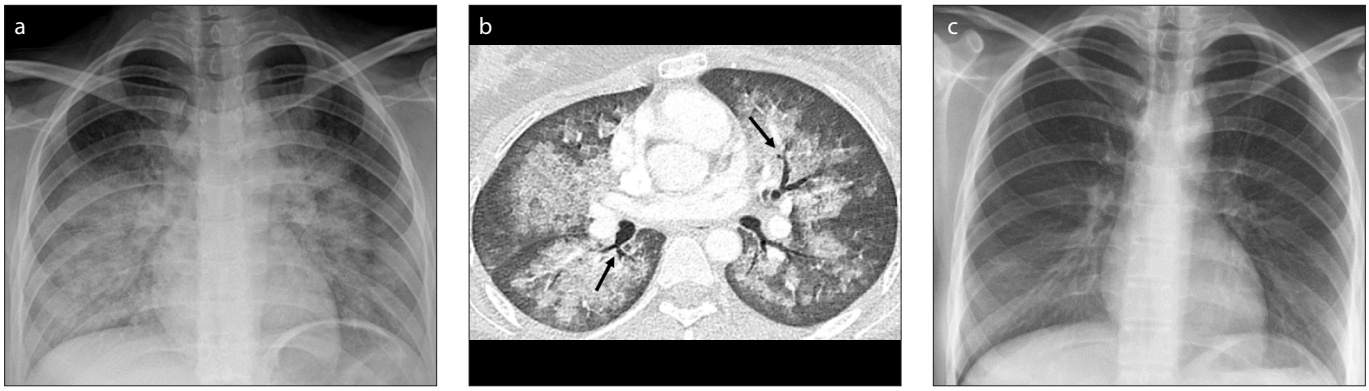


Figure 1. a–c. A 30-year-old woman with a history of melanoma undergoing HDIL-2 therapy presented with dyspnea. Chest radiograph **(a)** shows bilateral diffuse air-space opacities. Bilateral costophrenic angles are spared. Axial chest CT image **(b)** demonstrates bilateral ground-glass opacities and air bronchograms *(arrows)*. The heart is normal in size. The findings were consistent with HDIL-2 induced pulmonary edema. HDIL-2 therapy was stopped. Chest radiograph obtained two weeks later **(c)** reveals the resolution of findings.

nately, there has been mixed data revolving around this therapy. There were attempts to look at the relationship between adverse events observed with HDIL-2 and treatment effectiveness. Curti et al. (6) concluded that those who experienced adverse events had increased survival and better tumor control following treatment with HDIL-2.

The purpose of this pictorial review is to describe typical and atypical HDIL-2 related adverse events that can be identified on imaging. It is crucial for radiologists to be familiar with the adverse events associated with HDIL-2 therapy, which has a potential to be more commonly used in the future.

HDIL-2 related cardiothoracic adverse events

Multiple adverse events have been documented with the use of HDIL-2 such as hypotension, pre-renal azotemia, oliguria, and pulmonary edema (7). Pulmonary edema has been postulated to be caused by IL-2 activated NK cells and direct effect on vascular endothelium leading to capillary leak syndrome. It was determined that pulmonary edema was not due to renal insufficiency or fluid overload (7). Due to the prevalence of hypotension with HDIL-2, this therapy may be contraindicated in patients who have reversible ischemia on a cardiac stress test. Approximately 75% of patients undergoing HDIL-2 therapy may demonstrate radiologic signs of pulmonary edema (7). Only 25% of patients will go on to develop clinical signs and symptoms of pulmonary edema such as cough, dyspnea, tachypnea, and fever. Imaging findings that correspond to pulmonary edema include bilateral, symmetric interstitial opacities with thickened septal lines, air space opacification, and ground glass opacification (Fig. 1).

HDIL-2 therapy may cause cardiovascular toxicity which may manifest as arrhythmias, myocarditis, and cardiomyopathy. Takotsubo cardiomyopathy has been reported to be associated with HDIL-2 therapy. This particular reversible cardiomyopathy involves apical ballooning with transient left ventricle dysfunction (Fig. 2) (8). The presentation can be similar to acute coronary syndrome with ST-segment elevation in the anterior precordial leads or T wave inversion on electrocardiography (ECG). This disorder is characterized by akinesis, hypokinesis, or dyskinesis in the mid and apical segments of the left ventricular wall. No significant atherosclerotic lesions are identified during coronary angiography. Cardiac magnetic resonance imaging (MRI) can be used in the diagnosis of Takotsubo cardiomyopathy. The most characteristic finding is increased T2-signal intensity in the ventricular wall with a diffuse or transmural distribution, representing edema. Ventricular edema is observed in both the apical and mid planes of the left ventricle. Cine MRI can demonstrate motion abnormalities in the ventricular wall. The presence of apical akinesis leads to the ballooning of the left ventricle. Ventricular dysfunction may result in reduction in the ejection fraction which is reversible and transient (9).

Main points

- High-dose interleukin-2 (HDIL-2) therapy is used to treat metastatic melanoma and metastatic renal cell carcinoma (mRCC).
- HDIL-2 is associated with a broad spectrum of adverse events that can be radiologically identified including pulmonary edema, cardiomyopathy, hepatitis, cholecystopathy, pancreatitis, colitis, thyroiditis, and encephalopathy.
- Increased capillary permeability may be the underlying mechanism of HDIL-2 related adverse events.
- Although HDIL-2 therapy was more commonly used in the past, with new advances in immunotherapy to treat metastatic melanoma and mRCC, the reemergence of HDIL-2 therapy as a combination agent seems likely.

HDIL-2 related abdominal adverse events

HDIL-2 administration may induce hepatic toxicity. Although HDIL-2 related hepatitis by enzyme elevation is not common, it has been reported that this adverse event may require holding the HDIL-2 therapy (6).

Cholecystopathy associated with the use of HDIL-2 has been documented (Fig. 3). Powell et al. (10) reported cholecystopathy induced by IL-2 therapy in HIV infected patients. This pathology was diagnosed with ultrasound showing gallbladder wall thickening without presence of calculi. Symptoms abated when HDIL-2 infusion was stopped. On re-initiation of the treatment, patients had repeated cases of cholecystopathy (10). Gallbladder wall thickening without inflammation caused by gallstone may be caused by a variety of conditions including gallbladder diseases (acalculous cholecystitis, gallbladder carcinoma, adenomyomatosis), systemic diseases (liver cirrhosis, acute hepatitis, congestive right heart failure, hypoalbuminemia, ascites), and extracholecystic inflammation (pancreatitis, peritonitis, pyelonephritis) (11). This imaging finding should also be kept in

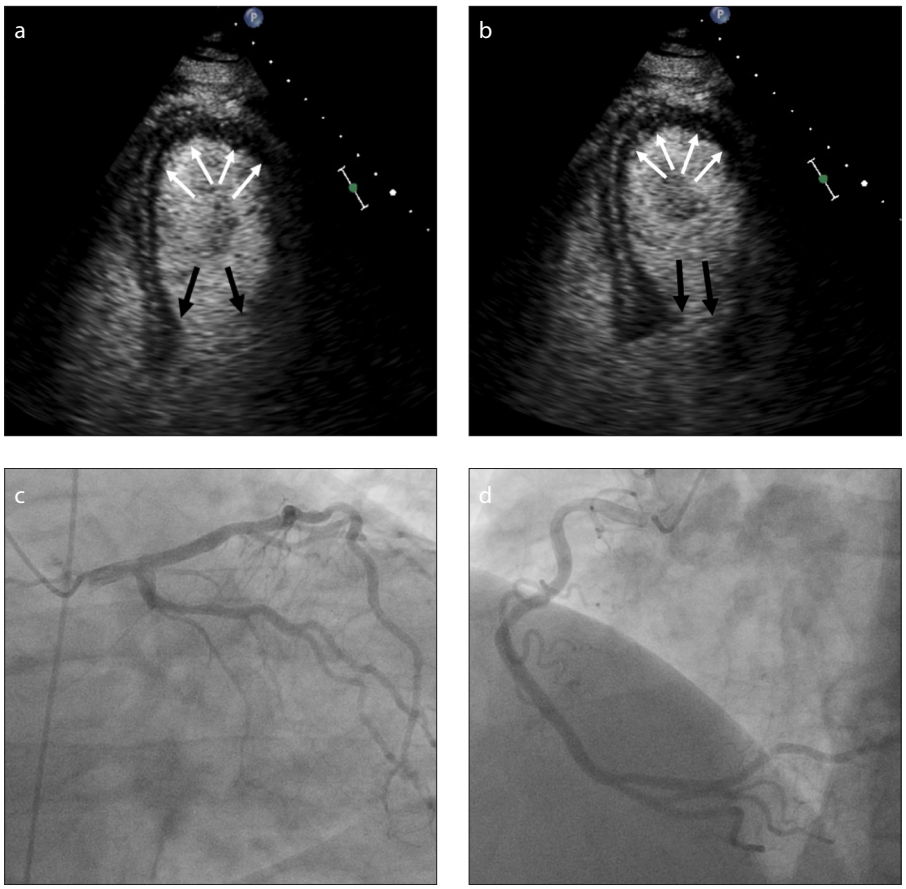


Figure 2. a–d. A 70-year-old man with a history of melanoma. While the patient was undergoing HDIL-2 therapy, he had tachycardia. Contrast-enhanced transthoracic echocardiography in apical four chamber view during diastole **(a)** shows dilation of the left ventricle more pronounced in the apex *(white arrows)*. The base of the left ventricle is shown with the *black arrows*. Contrast-enhanced transthoracic echocardiography in apical four chamber view during systole again **(b)** demonstrates dilation of the left ventricle more pronounced in the apex and showing no significant change in size when compared to diastole *(white arrows)*. However, the base of the left ventricle shows significant contraction *(black arrows)*. A coronary angiography was performed. Panel **(c)** shows normal coronary angiography with injection of the left main coronary artery. The left anterior descending and left circumflex artery are normal with no evidence of stenosis. Panel **(d)** shows normal coronary angiography with injection of the right main coronary artery. The right coronary artery and its branches are normal with no evidence of stenosis. The findings suggested Takotsubo cardiomyopathy and HDIL-2 was discontinued.

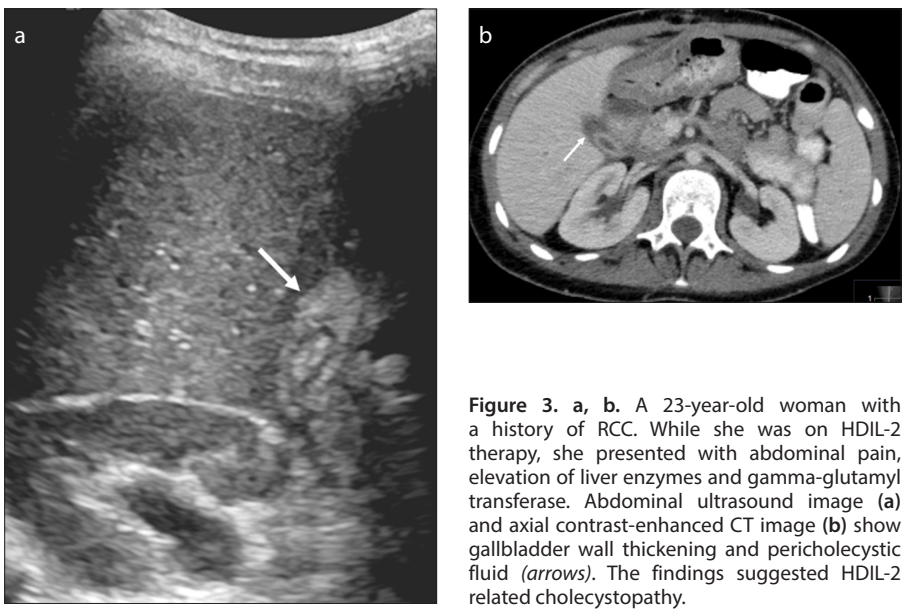


Figure 3. a, b. A 23-year-old woman with a history of RCC. While she was on HDIL-2 therapy, she presented with abdominal pain, elevation of liver enzymes and gamma-glutamyl transferase. Abdominal ultrasound image **(a)** and axial contrast-enhanced CT image **(b)** show gallbladder wall thickening and pericholecystic fluid *(arrows)*. The findings suggested HDIL-2 related cholecystopathy.

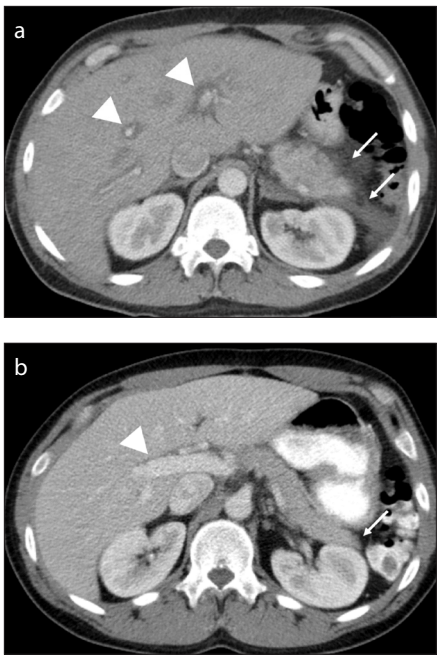
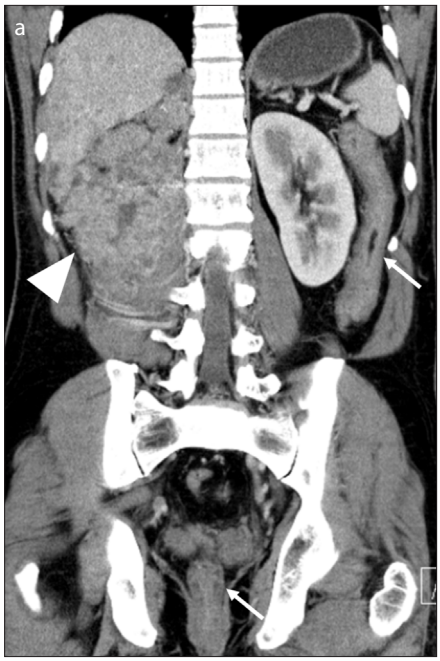


Figure 4. a, b. A 34-year-old man with a history of melanoma undergoing HDIL-2 treatment presented with abdominal pain. Axial contrast-enhanced CT image **(a)** shows edema and swelling of the pancreatic tail with peripancreatic fluid and fat stranding *(arrow)*. The findings were consistent with HDIL-2 related pancreatitis. Additionally, prominent periportal edema is noted *(arrowhead)*. HDIL-2 therapy was discontinued. Axial CT image obtained 1 month later **(b)** demonstrates resolution of the findings of pancreatitis *(arrow)* as well as periportal edema *(arrowhead)*.

mind in patients undergoing HDIL-2 therapy. Clinical history is very important for diagnostic determination of HDIL-2 related cholecystopathy and exclusion of other causes of gallbladder wall thickening (12). The underlying mechanism of HDIL-2 induced cholecystopathy is not clear, but it suggested that hypoalbuminemia caused by HDIL-2 therapy might contribute to it (10). A similar phenomenon was documented with symptomatic appendiceal wall thickening in an HIV infected patient due to HDIL-2 therapy (13). This entity may be observed in patients who present with right lower quadrant pain without leukocytosis. Ultrasound may demonstrate a swollen appendix without secondary inflammation. Symptoms are expected to resolve after cessation of HDIL-2 therapy.

HDIL-2 related pancreatitis has been documented and cases have been found to promptly resolve with withdrawal of HDIL-2 (14). IL-2 is a proinflammatory agent that stimulates the release of various inflammatory cytokines. It is thought that this characteristic of IL-2 might increase subclini-



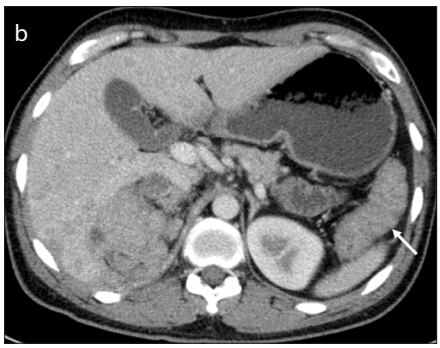


Figure 5. a, b. A 42-year-old man with with a history of renal cell carcinoma (RCC) and right nephrectomy, undergoing HDIL-2 therapy presented with diarrhea. Coronal contrast-enhanced CT image **(a)** demonstrates a large recurrent mass within the surgical bed that invades the right iliopsoas muscle *(arrowhead)* and liver metastases. Note the diffuse bowel wall thickening of the descending colon and rectum *(arrows)*. Axial contrast-enhanced CT image **(b)** shows diffuse bowel wall thickening of the descending colon *(arrow)*. The findings indicated HDIL-2-related colitis after the exclusion of infectious and inflammatory causes.

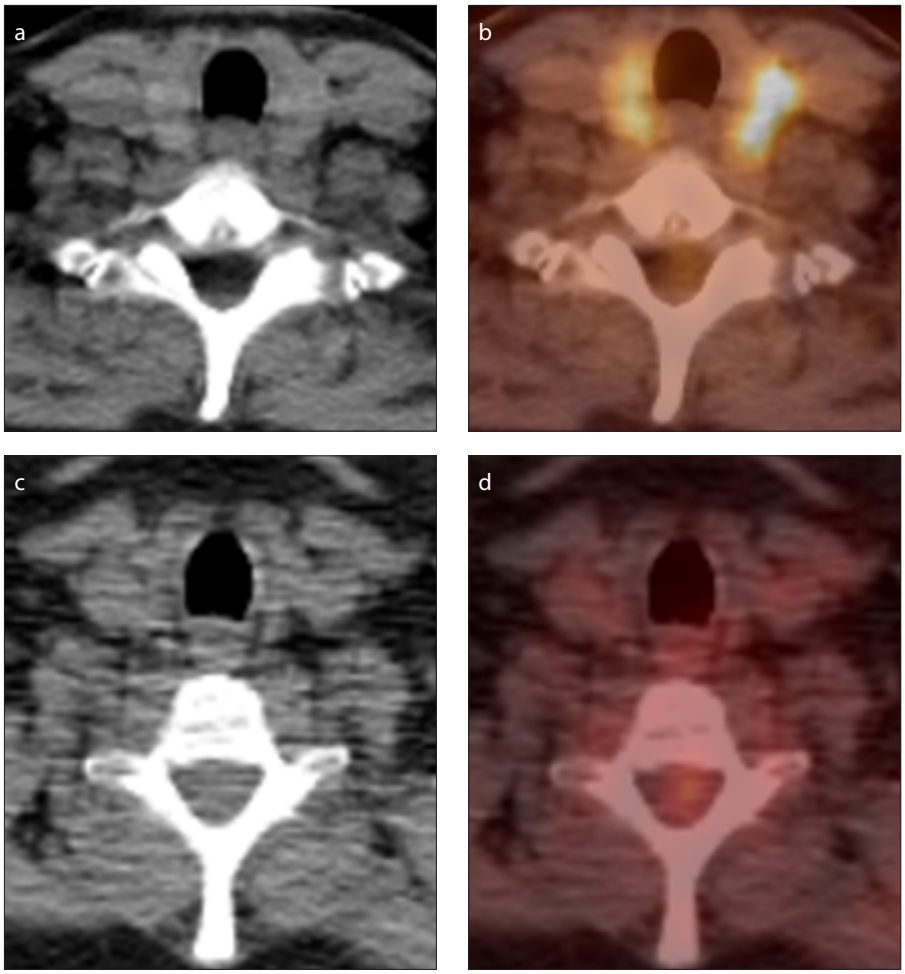


Figure 6. a, b. A 54-year-old woman with a history of melanoma. The patient received HDIL-2 therapy. Axial CT image of a restaging FDG-PET/CT scan **(a)** shows that the thyroid gland is normal in size. Axial fused FDG-PET/CT image **(b)** demonstrates diffusely increased FDG uptake within the thyroid gland, representing HDIL-2 related thyroiditis. Axial CT image of a restaging FDG-PET/CT scan obtained 21 months later **(c)** shows the atrophic thyroid gland. Axial fused FDG-PET/CT image **(d)** demonstrates resolution of metabolic activity in the thyroid gland.

cal or chronic pancreatic inflammation or trigger the immune recognition of normal pancreatic cells leading to pancreatitis (14). Patients with HDIL-2 related pancreatitis may present with acute abdominal pain. Increase in lipase and amylase levels may be observed. HDIL-2 associated pancreatitis may be radiologically identified. Computed tomography (CT) findings include focal or diffuse pancreatic enlargement, decreased enhancement of the pancreas, and peripancreatic fat stranding (Fig. 4).

Colitis can occur following HDIL-2 therapy (15). Additionally, bowel perforations have been reported in patients who received anti-CTLA-4 antibody and subsequently HDIL-2 (16). Imaging findings can be helpful in making the diagnosis of HDIL-2 related colitis. CT findings typically include marked circumferential thickening of the bowel wall. Pericolonic stranding and fluid may be present (Fig. 5). Also, pneumatosis may be identified. In severe cases, there may be abscess formation, intramural perforation, intestinal necrosis, or hemorrhage. The underlying mechanism of colitis and perforation during HDIL-2 therapy is not known. Yet, early use of systemic corticosteroids or other immunosuppressants has been suggested to control diarrhea and prevent bowel perforation when HDIL-2 related colitis is suspected (15).

HDIL-2 related endocrine adverse events

Thyroid dysfunction (both hypothyroidism and hyperthyroidism) has been reported following the HDIL-2 therapy, with the frequent development of anti-thyroid antibodies (17). Studies have demonstrated that thyroid dysfunction may resolve after completion of HDIL-2, although patients with moderate or severe hypothyroidism require thyroid replacement therapy. It is recommended that thyroid function should be evaluated in cancer patients receiving HDIL-2 therapy. Immune-related thyroiditis can be radiologically detected especially in the restaging or follow-up imaging studies. In cases of hyperthyroidism, diffusely enlarged and hypoenhancing and/or hypodense thyroid gland may be observed on CT scans. Subsequently, once hypothyroid-

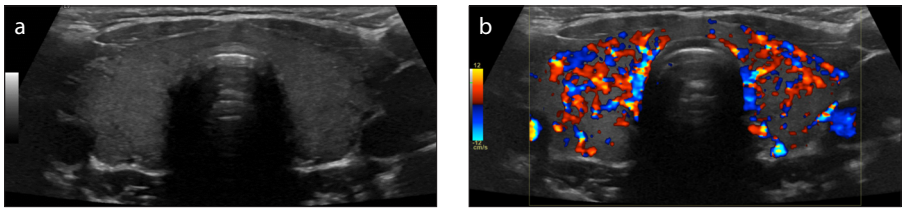


Figure 7. a, b. A 39-year-old man with metastatic RCC treated with HDIL-2. Ultrasound image **(a)** shows that the thyroid is mildly heterogeneous and hypoechoic. Color Doppler US image **(b)** demonstrates diffusely increased vascularity in the gland, consistent with thyroiditis. Thyroid function tests showed elevated thyroid stimulating hormone and low T4 levels. The patient was started on levothyroxine.

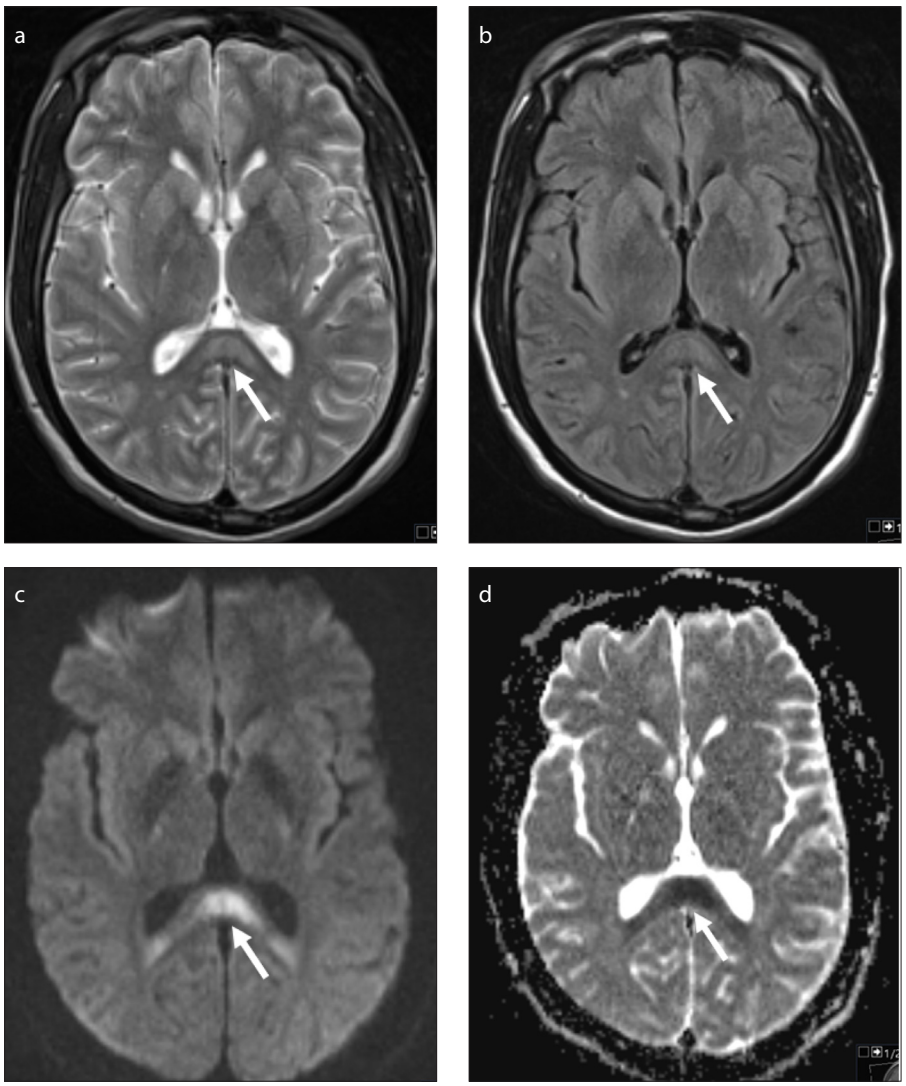


Figure 8. a–d. A 44-year-old woman with metastatic melanoma undergoing HDIL-2 therapy presented with altered mental status and gait instability. Axial T2-weighted image **(a)** and axial FLAIR image **(b)** demonstrate hyperintense lesion in the splenium of the corpus callosum *(arrows)*. Diffusion-weighted image **(c)** and ADC map **(d)** reveal diffusion restriction of the lesion *(arrows)*. The findings suggested HDIL-2 related encephalopathy. The patient's symptoms resolved following the cessation of HDIL-2 therapy.

ism occurs, the gland may appear diffusely hypodense and decreased in size. Newly identified diffuse 18F-fluorodeoxyglucose (FDG) uptake on PET/CT might represent thyroid dysfunction (Fig. 6) (18). Ultrasound could be performed when immune-related thyroiditis is suspected, either clinically or on CT or FDG-PET/CT. Findings include a diffusely enlarged gland, with micronodular pattern, demonstrating normal, increased, or decreased vascularity on Doppler US, resembling Hashimoto's thyroiditis (Fig. 7).

HDIL-2 related neurological adverse events

HDIL-2 therapy is associated with many neurological adverse events such as confusion, disorientation, anxiety, lethargy, altered sleep patterns, changes in behavior, and cerebrovascular ischemia (19, 20). The use of HDIL-2 in patients with brain metastases has been avoided due to potentially increased intracranial pressure from edema caused by HDIL-2 induced capillary leak syndrome. However, it has been reported that carefully selected patients with brain metastases may safely receive HDIL-2 (20). MRI findings suggesting embolic infarcts or acute encephalopathy may be helpful in the diagnosis of HDIL-2 related neurological adverse events (Fig. 8).

Conclusion

With new advances in the field of immunotherapy to treat metastatic melanoma and mRCC, the reemergence of HDIL-2 therapy as a combination agent seems likely. Due to the reintroduction of this therapy, it is important for radiologists to consider the adverse events associated with HDIL-2 treatment as they can be radiologically identified.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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