The CT halo sign in pulmonary metastases following adoptive cell therapy for metastatic melanoma: possible clinical significance

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Purpose

Melanoma appears to be unique among human cancers because of its ability to induce significant lymphocyte production with anti-tumor activity as it grows, specific for autologous tumor-associated antigens (1;2). These tumor infiltrating lymphocytes (TIL) can thus be used to develop immunotherapeutic tools. Adoptive cell therapy (ACT) refers to the procedure by which anti-tumor lymphocytes are identified, grown ex vivo and then infused back into the cancer patient.

Melanoma is also one of the few cancers with a typical tendency to bleed, partly accounting for hyperintense T1WI and hyperdense CT lesions. That may also be the cause for the appearing of a CT halo sign, in lung metastases, rarely reported in patients with melanoma.

The CT halo-sign refers to a pulmonary nodule or consolidation surrounded by a zone of ground-glass attenuation. The halo-sign is mainly observed in infectious diseases such as aspergillosis, and in inflammatory non-infectious conditions, such as Wegener's granulomatosis (Table 1) (3). The histo-pathological correlation of the halo sign is thought to be a peri-lesional hemorrhage, possibly related to microvascular injury due to inflammation, infarction or weakness of the neovascular tissue (4). It is rarely seen in neoplastic primary and secondary lung malignancies that are highly aggressive, such as squamous cell carcinoma and metastatic melanoma, respectively (3;5). In the later it may be, as noted earlier, due to the highly vascular nature of melanoma, resulting in hemorrhage surrounding the lung nodules (6).

In this study, we describe the appearance of halo-sign in lung metastatic melanoma following adoptive cell therapy with TIL and discuss its possible role as a predictor of response. As far as we know this is the first such a description.

Images for this section:
Infectious diseases
  Fungus; aspergillosis, mucormycosis, candidiasis
  Mycobacteria; tuberculosis, Mycobacterium avium complex
  Rickettsia; Coxiella burnetti
  Virus; herpes simplex virus, varicella-zoster virus, cytomegalovirus
  Septic embolism
Neoplastic diseases
  Primary tumours; squamous cell carcinoma, Kaposi sarcoma, bronchioloalveolar carcinoma, adenocarcinoma
  Metastatic tumours; angiosarcoma, choriocarcinoma, osteosarcoma, melanoma, hydatidiform mole, metastatic tumours from gastrointestinal malignancies
  Lymphoproliferative disorders
Non-neoplastic, non-infectious, inflammatory diseases
  Wegener’s granulomatosis
  Eosinophilic lung disease
  Pulmonary endometriosis
  Organizing pneumonia
  Hypersensitivity pneumonitis
  Iatrogenic injury; transbronchial lung biopsy, catheter-induced pulmonary pseudoaneurysm

Table 1: List of diseases showing the CT halo-sign (modified from (3))
Methods and Materials

Study design - An institutional review board-approved retrospective observational study was conducted by reviewing the chest CT studies of melanoma patients with lung metastases. The pre- and post- TIL treatment CTs were assessed according to the RECIST (versions 1.0 and 1.1). The appearance of a halo sign was noted as well. CT findings were correlated with clinical response.

Population - All patients received chemobiotreatment (IL-2, cisplatin and dacarbazine) as a first line therapy. Failure of this treatment lead to second line treatment including myeloablation chemotherapy (cyclophosphamide and fludarabine) followed by IL-2 and TIL infusion.

Follow-up - The patients underwent clinical evaluation as well as sequential imaging consisting of baseline chest, abdomen and pelvis contrast enhanced computerized tomography (CT) scans. Follow-up CTs one month and three months after the TIL infusion and every three months thereafter were performed as well. The CT scans were conducted on a 64 multi-slice scanner.

Inclusion criteria were: (1) Metastatic melanoma with lung metastases at the initiation of the TIL infusion (2) Treatment with TIL in our center, (3) Pre- and post-treatment (at least one and three months after TIL infusion) chest CT scans and (4) At least six months follow-up after TIL infusion.

Data analysis - The study group was too small to calculate statistics, therefore we looked whether there are trends in the results.

Results

Study population - 72 patients were treated with TIL in our center between 1/2006 and 7/2011. 30 of them had lung metastases at initiation of TIL infusion, 29 of whom had pre and post treatment chest CT studies, and were included in the study, which included 21 men, 8 women with a mean age 52.8±11.5. One patient (MG) was treated with a second courses of TIL infusion after disease progression.

Clinical response to TIL - Twelve out of the 29 patients with lung metastases, treated with TIL, showed partial or complete response, according to the RECIST criteria. In four (a third) of these responders, we observed a halo sign on the post treatment CT, in some
of their pulmonary metastases. Sequential chest scans, showed either further decrease or no further change in the diameter of their lung metastases. Figures 1 and 2 show a CT halo sign in two different patients on the post treatment CT (figures 1B and 2B). A decrease in the diameter of these lesions, compared to baseline (figures 1A and 2A, respectively) is observed as well. Sequential chest scans, show further decrease (figures 1C and 2C) of the lung metastasis.

Such a halo sign was not observed on the post treatment CT in any of the patients that did not respond. The trend seems obvious that such a halo appearing following TIL therapy indicates good response.

Despite a correlation between the appearance of the halo sign and best clinical response, there was no correlation between its appearance and the duration of the response as well as with overall survival.

**Images for this section:**

![Fig. 1](image)

**Fig. 1:** Axial CT images (lung window) of a 56-Y-old man with metastatic melanoma. A-Baseline scan: a metastatic nodule is seen in the left upper lobe (arrow). B - 1 month after TIL infusion: a halo sign surrounding the nodule is noted and the lesion decreased in size (arrow). C - 3 months after TIL infusion: further decrease in size of the nodule is observed.
Fig. 2: Axial CT images (lung window) of a 45-Y-old man with metastatic melanoma. A- Baseline scan: metastatic nodule is seen in the right upper lobe. B - 1 month after TIL infusion: a halo sign is observed around the metastatic nodule (arrow). C - Follow-up chest CT 3 years post TIL infusion demonstrates a small residual (arrow).
Conclusion

A CT halo sign was detected in our melanoma patients following TIL, a CT appearance not described previously. Moreover, it was seen only in those who responded to therapy by regression of their pulmonary metastases.

The appearance of a halo sign in pulmonary metastatic melanoma in our patients could represent lymphocyte infiltration, as well as tumor necrosis and hemorrhage resulting from the TIL anti-tumoral activity. None of the patients, who had progressive disease in their lung, showed this sign, suggesting that the halo sign may serve as an imaging marker for anti-tumoral activity of the TIL.

Assessment of the change in tumor burden is an important component of the clinical evaluation of cancer therapeutics. These standard criteria were designed to capture the effects of chemotherapeutic agents and are dependent on tumor shrinkage to demonstrate activity, as assessed by the RECIST. The response patterns observed with immunotherapeutic agents, however, extend beyond those of chemotherapeutic agents. Appearance of halo around a solid pulmonary lesion, as seen in our study, makes accurate assessment of lesion dimensions challenging. Recently, immune-related response criteria (irRC) were defined to capture the unique response patterns of immunotherapeutic agents "other than shrinkage" response patterns. In particular, they allow for incorporation of measurable new lesions into "total tumor burden" and comparison of this variable to baseline measurements (7).

In conclusion, appearance of a halo-sign after TIL treatment for metastatic melanoma may imply ongoing anti-temporal activity and may predict regression of the lesions, and hence response. This is however, a preliminary report with a small number of patients. Further studies are needed, with a possible statistical significance, in order to confirm this trend and assess the added value of the halo sign in the response evaluation of patients undergoing ACT therapy with TIL.

References


Personal Information