

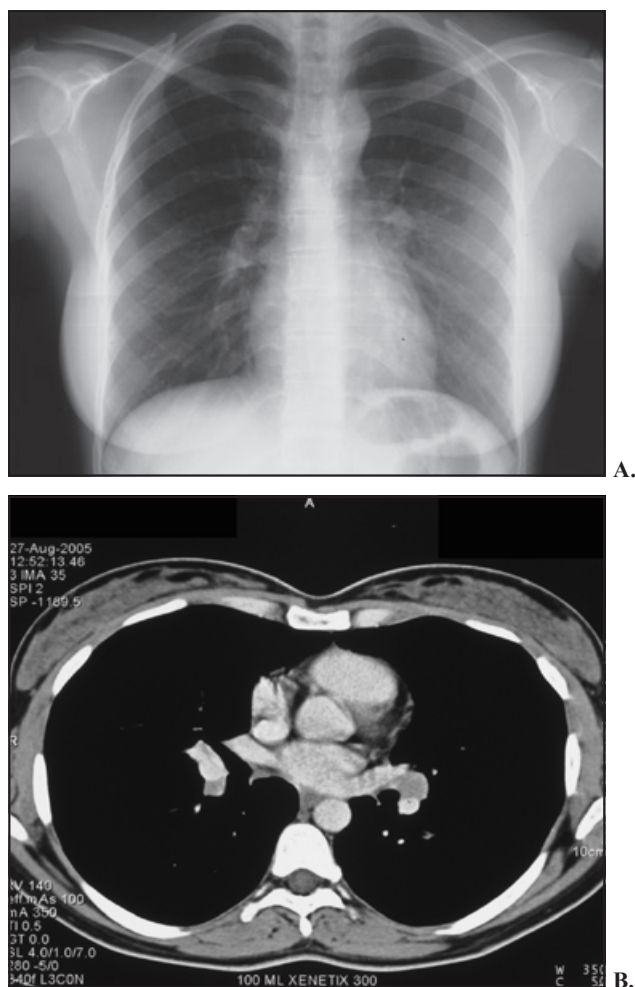
## Interferon-induced sarcoidosis with osseous involvement in a patient with melanoma

**To the Editor:** Interferons are widely used in the treatment of both malignant and nonmalignant diseases. One rare complication, attributable to the immunomodulatory effect of interferon (IFN) treatment is the triggering or exacerbation of sarcoidosis [1]. We present the scintigraphic and radiographic imaging findings of a patient that developed sarcoidosis with bone involvement mimicking metastatic disease during the course of adjuvant IFN-alpha treatment for malignant melanoma.

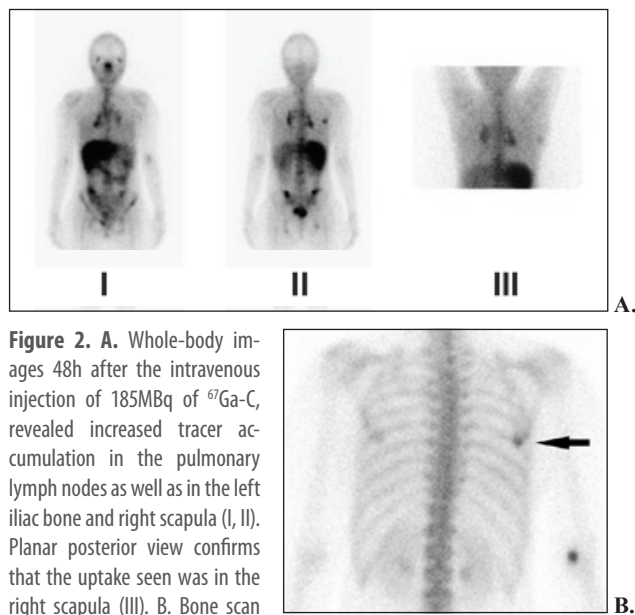
A 32 years old woman was diagnosed with a superficial left tibial melanoma, metastatic to the inguinal lymph nodes (Clark level IV; Breslow tumor thickness 1.82mm). Since the primary tumour had more than 0.75mm thickness the patient underwent re-excision of the primary lesion with radioguided sentinel lymph node biopsy [2], which was positive for micrometastases and subsequently underwent dissection of

the lymph nodes of the left groin. She received adjuvant treatment with IFN-alpha. A chest X-ray taken prior to IFN-alpha treatment was unremarkable. Three months later, the patient presented with dry cough and mild dyspnea on exertion. Physical examination was unremarkable; a chest X-ray was inconclusive, with possible left hilar enlargement (Fig. 1A). Chest computed tomography (CT) showed enlarged mediastinal and hilar lymph nodes (Fig. 1B) as well as a few bilateral small nodules. Pulmonary function tests showed normal spirometry, lung volumes were at lower limit of normal and diffusing capacity was moderately decreased at 79% of predicted.

The patient was referred for a gallium-67 citrate ( $^{67}\text{Ga-C}$ ) scan (Fig. 2A), which showed the characteristic "Lambda sign" indicative of sarcoidosis as well as foci of increased accumulation in the right scapula and left iliac bone. A subsequent technetium-99m methylene diphosphonate ( $^{99\text{m}}\text{Tc-MDP}$ ) scan revealed the same skeletal lesions (Fig. 2B). Magnetic resonance imaging (MRI) of the thorax (Fig. 3) and pelvis was concordant with the  $^{67}\text{Ga-C}$  and  $^{99\text{m}}\text{Tc-MDP}$  scan findings. The patient's history of malignant melanoma and the anatomical and functional imaging findings led to the clinical suspicion of osseous metastases. Bronchoalveolar lavage showed lymphocytosis, leukocytosis and macrophages with elevated CD4/CD8 ratio. Moreover, transbronchial needle aspiration lung biopsy revealed non-caseating granulomas whereas bone biopsy of the right scapula was negative for malignancy and showed non-caseating granulomas, consistent with sarcoidosis. Treatment with IFN-alpha was

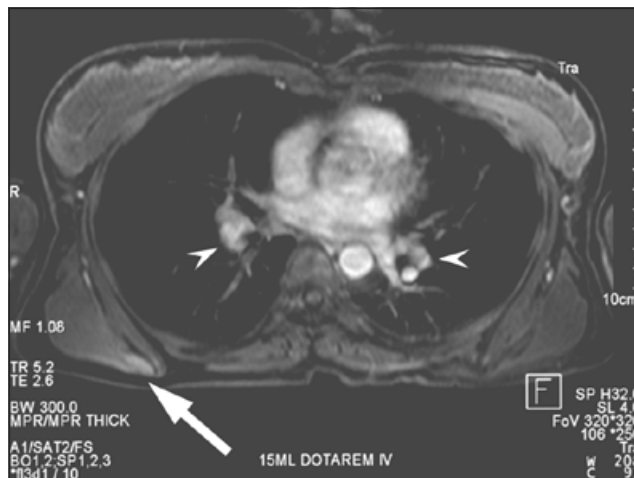


**Figure 1. A.** Chest X-rays with questionable left hilar lymphadenopathy. **B.** Axial chest CT scan (mediastinal window) demonstrates hilar lymphadenopathy.



**Figure 2. A.** Whole-body images 48h after the intravenous injection of 185MBq of  $^{67}\text{Ga-C}$ , revealed increased tracer accumulation in the pulmonary lymph nodes as well as in the left iliac bone and right scapula (I, II). Planar posterior view confirms that the uptake seen was in the right scapula (III). **B.** Bone scan with  $^{99\text{m}}\text{Tc-MDP}$  planar posterior images of the thorax shows intense tracer uptake in the right scapula (arrow). The increased activity in the area of the right basilic vein is due to residual radiopharmaceutical concentration after the injection.

withdrawn; the dyspnea and dry cough subsided within several weeks and three months later the patient had complete clinical remission. Pulmonary function tests were normal and a follow-up MRI after 9 months showed resolution of both hilar lymphadenopathy and osseous lesions. The patient, six years after initial presentation, remains in clinical remission. Thus, a diagnosis of interferon-induced sarcoidosis in melanoma adjuvant treatment was established.



**Figure 3.** Axial thoracic MRI (three-dimensional volumetric interpolated breath-hold examination technique; 3D-VIBE) showed hyperintense signal in the right scapula (arrow) and enlarged hilar lymph nodes (arrowheads).

It has been recently recognized that IFN- $\alpha$  can induce or exacerbate sarcoidosis, presumably through its ability to stimulate the T-helper cell type 1 immune response leading to granuloma formation, which is also involved in the pathogenesis of sarcoidosis, resulting in clinical disease in susceptible individuals [1, 3, 4]. Reported IFN- $\alpha$ -induced sarcoidosis occurs from 2 to 168 weeks after starting treatment [3]. The most common organs involved are the lungs, lymph nodes and the skin. After discontinuation of IFN- $\alpha$ , and with no other treatment received, the prognosis of sarcoidosis in the vast majority of cases is favourable; for some patients corticosteroids are needed [3, 4]. Most cases of IFN-induced sarcoidosis have been described in patients treated with IFN for chronic hepatitis C; sarcoidosis has also been reported in patients treated with IFN for chronic hepatitis B, renal carcinoma, chronic myelogenous leukaemia, multiple sclerosis, multiple myeloma, and lymphoma [1, 3, 4]. Eleven cases of sarcoidosis have been reported in IFN-treated patients with malignant melanoma [5]. To the best of our knowledge IFN-induced sarcoidosis with bone involvement has not been reported previously.

Scintigraphy with  $^{67}\text{Ga}$ -C has the advantage of detecting both pulmonary, with the characteristic lambda and/or panda uptake pattern [6] and extrapulmonary foci of sarcoidosis, assisting diagnosis. Biopsy is mandatory for the diagnosis of the disease. Among the newer functional imaging modalities, fluorine-18 fluoro-deoxyglucose ( $^{18}\text{F}$ -FDG) PET is not useful in diagnosing sarcoidosis, since it shows nonspecific uptake, both pattern and intensity-wise, although it is useful in monitoring disease progression or remission [7]. Although sarcoidosis is a systemic disease, osseous involvement, mostly in the small bones of the hands and feet is relatively uncommon, noted in 5% of patients, although extremes of

1% to 13% have been reported [8]. In some cases sarcoidosis may mimic metastatic dissemination [8, 9]. Although bone scans and MRI are more sensitive than either radiographs or  $^{67}\text{Ga}$ -C scintigraphy in the detection of osseous sarcoidosis, they are also non-specific [10].

*In conclusion* treatment with IFN- $\alpha$  may induce sarcoidosis not only in the lung but also in the skeleton; when restaging patients with malignant diseases it may mimic metastatic bone disease leading to diagnostic pitfalls.

*The authors have no conflicts of interest.*

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