



Case Report

# Osteoblastic Flare During Chemo-Immunotherapy in Small Cell Lung Cancer: Do Not Be Misled!

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## Abstract

**Introduction:** “Osteoblastic flare” is defined as a temporary increase in bone tracer uptake associated with therapy response in patients without previously detected bone metastases. Hypothetically these apparently “new osteoblastic” lesions are not visible at baseline and are radiologically detected only after a bone sclerotic healing reaction has appeared, for this reason it does not indicate disease progression, but the healing of previously inconspicuous lesions. This phenomenon has been described in several solid tumours as response to antineoplastic treatments; however, it had never been reported in patients with ES-SCLC treated with chemo-immunotherapy.

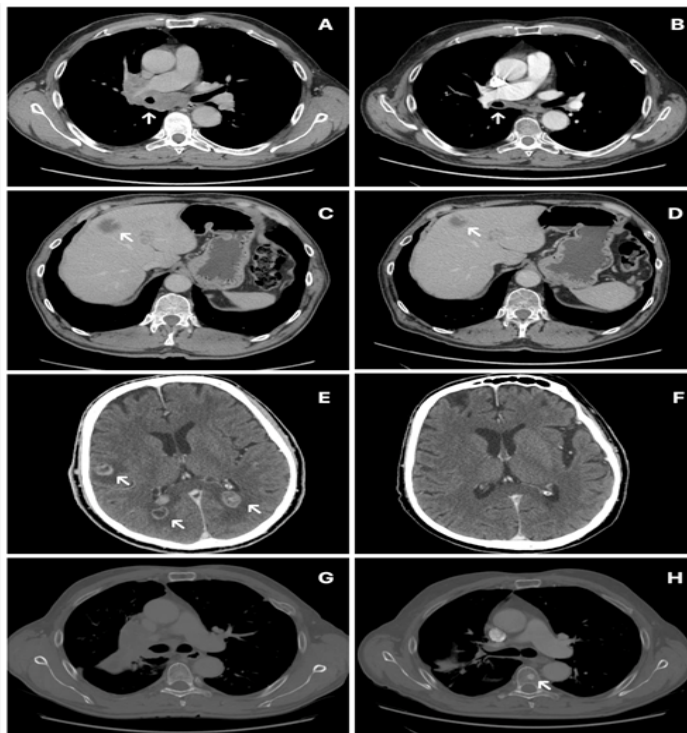
**Methods:** The Computed Tomography scans (CTs) of five patients with ES-SCLC treated with first-line chemo-immunotherapy with Atezolizumab, Carboplatin and Etoposide, were retrospectively reviewed to analyse the bone response to treatment compared with the response of the visceral tumour.

**Results:** On reassessment CTs the development of new onset osteoblastic lesions was associated with a partial response in the other disease sites. In each case, osteoblastic lesions, developed during therapy, were considered as a response reflecting bone repair and efficacy of the treatment. Therefore, the maintenance therapy was continued obtaining a temporary stability of the disease. In view of the increasing use of chemo-immunotherapy in this setting, it is important not to confuse this phenomenon with disease progression, in order to avoid discontinuation of the maintenance immuno-therapy treatment, which the patient could benefit from.

**Keywords:** Chemo-Immunotherapy; ES-SCLC; Osteoblastic-Flare

## Introduction

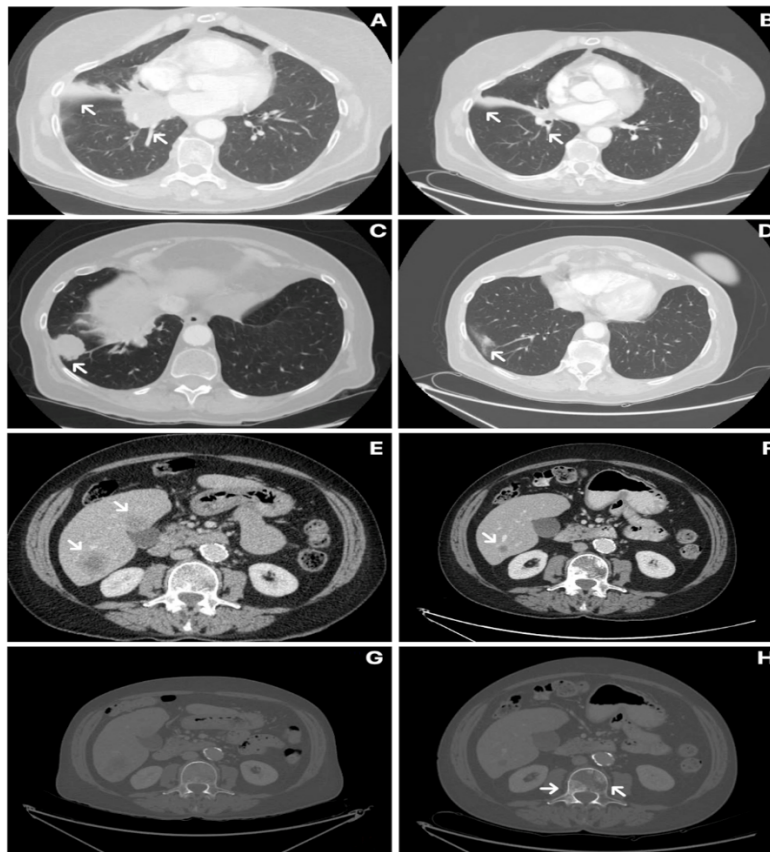
Small cell lung cancer (SCLC) represents approximately 13-16% of annual lung cancer diagnoses world-wide. The ability of SCLC tumour cells to disseminate early explains why 60-70% of cases presents with extensive stage (ES) disease, with bone and liver being predominant sites for metastatic involvement. Reliable detection of bone and bone marrow metastases, which affect 40-60% of patients, remains an unsolved issue in SCLC staging. The prognosis of ES-SCLC is dismal, with 5-year overall survival (OS) less than 7% [1,2]. The life expectancy of ES-SCLC patients had not improved in the last three decades, till the publication of two recent clinical trials (CASPIAN and Impower-133) showed how the addition of anti-programmed death ligand (PD-L1) therapy to chemotherapy led to a modest OS benefit over chemotherapy alone [3,4]. In the past decades, the appearance of bone metastases (either osteolytic or osteoblastic) during treatment was usually qualified as disease progression. More recently, bone flare reaction, including the onset of new osteoblastic lesions, has been redefined as a sign of response to antineoplastic treatment. If misunderstood as skeletal progression, this finding could lead to erroneous therapy discontinuation, changing the disease clinical course eventually giving a negative effect on patients' clinical outcome. To our best knowledge, bone flare reaction had never been reported in patients with ES-SCLC treated with chemo-immunotherapy. Thus, we retrospectively reviewed the computed tomography scans of five patients with ES-SCLC treated with first-line Atezolizumab, Carboplatin and Etoposide at the Division of Oncology of Modena University Hospital evaluating bone and visceral tumour response to treatment.



**Figure 1:** Base-line contrast-enhanced CT-scan showed a solid expansive hilar process on the right (A), liver (C) and brain (E) lesions (arrows), while no bone metastases were detected (G). The reevaluation CT-scan after 4 courses of chemo-immunotherapy showed the reduction of the pulmonary (B), liver (D) and brain (F) lesions (arrows), but the onset of osteoblastic lesions (H) in the dorso-lumbar vertebrae (arrow). (CT: Computed Tomography).

### Case 1

On February 2021, a former smoker 68-year-old white man was diagnosed with ES-SCLC (liver, nodes and brain metastases). Bone metastases could not be detected at diagnosis [Figure 1]. He received four courses of first-line chemo-immunotherapy followed by Atezolizumab as maintenance immunotherapy. After first cycle patient underwent surgery to reduce a pertrochanteric fracture (consequence of accidental fall). Neoplastic cell infiltration was not detected on the surgical specimen. At first evaluation, after three months of chemo-immunotherapy, and before the beginning of immunotherapy maintenance computed tomography (CT) scans showed the onset of multiple osteoblastic lesions that were not confirmed by 18-fluorodeoxyglucose PET (18-FDG-PET). A marked reduction in all the previously identified metastases, included disseminated brain lesions, were reported [Figure 1]. In view of the good response elsewhere, the osteoblastic lesions were considered an osteoblastic response to treatment and immunotherapy maintenance was continued until august 2021 when brain progression was documented, and the patient died shortly after.

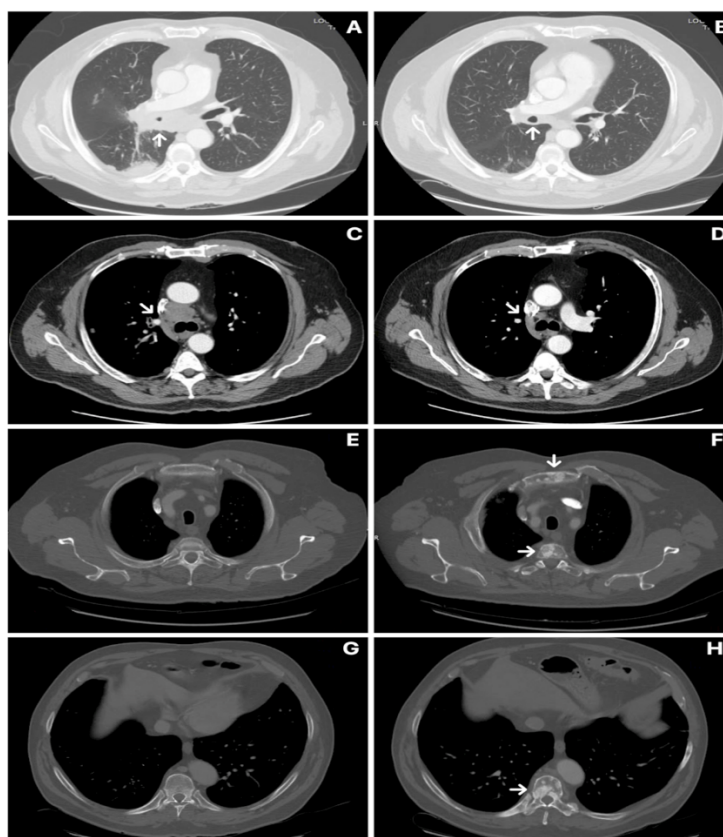


**Figure 2:** Base-line contrast-enhanced CT-scan showed a solid expansive hilar process on the right (A), a smaller one at the homolateral lower lobe (C) and liver (E) lesions (arrows), while no bone metastases were detected (G). The reevaluation CT-scan after 4 courses of chemo-immunotherapy showed the reduction of the pulmonary (B, D) and liver (F) lesions (arrows), but the onset of osteoblastic lesions (H) in the dorso-lumbar vertebrae (arrows). (CT: Computed Tomography).

### Case 2

On February 2021 an active smoker 74-year-old woman was diagnosed with an ES-SCLC (liver, pleural effusion and adrenal glands). No bone metastases were detected at diagnosis. She underwent first-line chemo-immunotherapy followed by Atezolizumab maintenance. At first evaluation, after 3 months of chemo-immunotherapy, computed tomography scans showed the onset of osteoblastic lesions [Figure 2]. All phosphocalcic metabolites on blood tests were normal. A significant reduction in all the previously identified metastatic sites was described [Figure 2]. To better define the nature of the new bone lesions, 18-FDG-PET imaging was performed with no increase of tracer uptake reported in the multiple vertebral lesions. Due to worsening back-pain, a spinal Magnetic Resonance

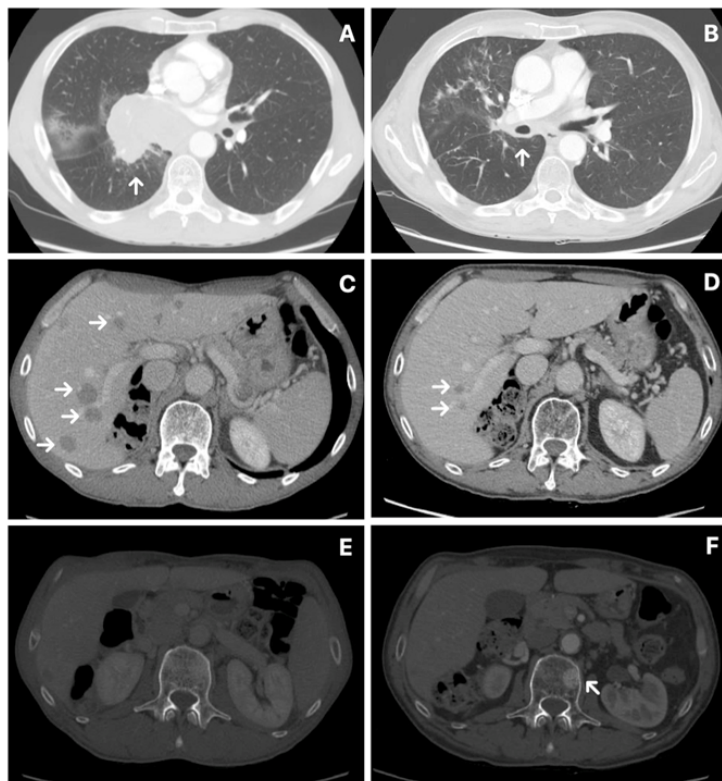
Imaging (MRI) was performed which demonstrated D12 vertebral-collapse and osteothickening lesions of D11, and L2-L5. After neuro-radiologist image revision, the palliative radiotherapy program was excluded as the bone lesions seemed to be related to osteoporosis. Thus, the patient underwent D12 vertebroplasty. Also, L3 bone biopsy was performed but no tumour cells were detected on histological specimen. The second evaluation by CT scan, performed 3 months later after 4 courses of immunotherapy maintenance, showed a substantial stable disease, so the patient continued maintenance with Atezolizumab for a total of 12 courses until progression was detected in January 2022.



**Figure 3:** Base-line contrast-enhanced CT-scan showed a solid expansive hilar process on the right (A) and a homolateral paratracheal adenopathy (C, arrows), while no bone metastases were detected (E, G). The reevaluation CT-scan after 4 courses of chemo-immunotherapy showed the reduction of the pulmonary lesion (B) and the adenopathy (D, arrows), but the onset of osteoblastic lesions in all skeletal segments included in the scan volume (sternal manubrium and dorsal vertebrae (F, H, arrows)). (CT: Computed Tomography).

### Case 3

On February 2021 an active smoker 63-year-old man was diagnosed with an ES-SCLC with bone involvement showed by 18-FDG-PET, without detectable bone lesions on CT scan [Figure 3]. Patient underwent standard first-line chemo-immunotherapy for four courses followed by Atezolizumab as maintenance immunotherapy. The first reevaluation CT scan made after 3 months of therapy, detected osteosclerosis at the sites of bone metastases previously evidenced by 18-FDG-PET, and a significant reduction in all other previously identified metastases sites [Figure 3]. All phosphocalcic metabolites on blood remained normal. The increased sclerosis was considered likely to be an osteoblastic healing response to immunotherapy and for this reason he has been continuing immunotherapy for a total of 3 courses until progression of intrathoracic disease (pulmonary and lymph-nodes), liver, and bone disease, was documented by CT scan made in August 2021.



**Figure 4:** Base-line contrast-enhanced CT-scan showed a solid expansive hilar process on the right (A) and liver lesions (C, arrows), while no bone metastases were detected (E). The reevaluation CT-scan after 4 courses of chemo-immunotherapy showed the reduction of the pulmonary lesion (B) and liver lesions (D, arrows), but the onset of osteoblastic lesions in iliac bone, sacrum, dorsal/lumbar vertebrae, ribs and the sternum (dorsal vertebrae (F, arrow)). (CT: Computed Tomography).

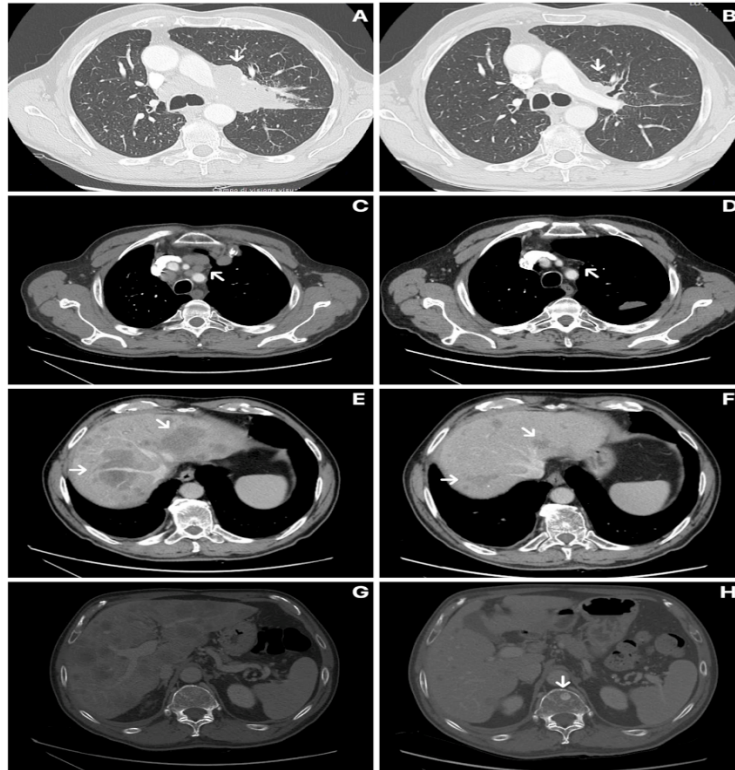
#### Case 4

On June 2021 an active smoker 61-year-old man was diagnosed with ES-SCLC with liver involvement [Figure 4]. The patient was enrolled in a research protocol so was initially treated with standard first-line chemo-immunotherapy combined with an anti-angiogenic agent (which was suspended after the first course due to an arterial thrombosis). After 4 courses of therapy, the CT scan showed an important reduction of lung lesion and liver metastases together with the unexpected appearance of multiple osteoblastic bone lesions (iliac bone, sacrum, dorsal/lumbar vertebrae, ribs and the sternum) [Figure 4]. The patient reported no pain at any of the involved bone sites; rather he reported an overall clinical benefit. Based on the experiences of cases 1-3 described above, the osteoblastic response was considered as a potential tumour flare to chemo-immunotherapy, so the patient continued Atezolizumab as maintenance therapy for 6 courses maintaining a stable disease, until he was re-evaluated in February 2022 with a CT-scan which documented progression of brain, lung and bone disease. The patient died few months later.

#### Case 5

On July 2021 a 69-year-old former smoker, man was diagnosed with ES-SCLC. He was already known for a previous diagnosis of lung adenocarcinoma stage IIA treated with surgery and subsequent adjuvant chemotherapy five years earlier. After the ultrasound detection of liver metastases, a restaging CT-scan performed in June 2021, showed a large lesion in the left lung involving the ipsilateral pulmonary hilum. Loco regional lymph-nodes and liver were involved, while no bone metastases were described [Figure 5]. A liver biopsy was then performed. The pathology report was compatible with metastases from SCLC, therefore from July to September 2021 the patient received four cycles of first-line chemo-immunotherapy. On September 2021, the patient underwent to CT-scan reevaluation revealing remarkable response of the left lung lesion, loco regional lymph nodes and liver disease, but also the appearance of novel osteo thickening lesions of the ribs, rachis and pelvis [Figure 5]. Based on these findings, the patient started a maintenance therapy with

Atezolizumab that was withheld in December 2021 due to multiple districts disease progression. The patient died in April 2022 due to meningeal involvement.



**Figure 5:** Base-line contrast-enhanced CT-scan showed a solid expansive Para hilar process on the left (A), a homolateral paratracheal adenopathy (C) and liver lesions (E, arrows) while no bone metastases were detected (G). The reevaluation CT-scan after 4 courses of chemo-immunotherapy showed the reduction of the pulmonary lesion (B) the adenopathy (D) and liver lesions (E, arrows), but the onset of osteoblastic lesions in almost all skeletal segments included in the scan volume (D12 (H, arrow)). (CT: Computed Tomography).

## Discussion

Osteoblastic flare is a phenomenon defined as a temporary increase in tracer uptake associated with therapy response for previously undetected bone metastases and has been described as a healing response to effective cytostatic chemotherapy and hormonal therapy [5]. It has been defined for prostate, breast and small-cell-lung-cancer, as a definitive radiological increase in the quantity and density of lesions, while clinical remission is well documented [6-8]. These apparently “new osteoblastic” lesions are probably not visible at baseline and are radiologically detected only after a bone sclerotic healing reaction has appeared [9]. Tumor flare reaction has been previously described as unexpected side effect associated with immune checkpoint inhibitors (ICIs) in solid tumours [10]. To date it is still poorly understood and its incidence is underestimated. Comito F. et al reported an osteoblastic bone response mimicking bone progression during treatment with pembrolizumab in advanced cutaneous melanoma [11]. To our

knowledge, in lung cancer, only few cases of osteoblastic healing response have been reported and the majority of these reports described non-small-cell-lung cancer (NSCLC) patients. Bersanelli et al. detected [10] osteoblastic reactions on 43 patients treated with EGFR-TKis for EGFR mutated non-small-cell-lung cancer, showing different patterns: dimensional density increase of known osteosclerotic metastases, response to previously lytic lesions and onset of new osteosclerotic lesions [12]. Similar evidence was reported by Ansen S. et al in three patients treated with gefintib or erlotinib for stage IV adenocarcinoma with activating EGFR mutations [13,14]. Osteoblastic response mimicking bone progression during ceritinib treatment was also reported in ALK-rearranged NSCLC [15]. Krupitskaya et al. reported osteoblastic bone flare on F18-FDG PET in NSCLC patients receiving bevacizumab in addition to standard chemotherapy [16]. In ES-SCLC, Cosolo et al. reported two cases of a bone flare after 3 months of chemotherapy associated with a dramatic improvement in all metastatic sites [7]. Stattaus et al. in their retrospective

study on 24 patients, observed an osteoblastic healing response rate in 63% patients with newly diagnosed ES-SCLC during effective chemotherapy [5]; this reported frequency is remarkably higher than the rate reported for other tumour entities (i.e. 12% for breast cancer, 44% for prostate cancer). For the authors this could be explained by a high initial rate of occult bone marrow metastases and by a high responsiveness to chemotherapy than a high conversion rate of bone lesions into hyper sclerotic bone rings. Moreover, Fink et al. presented the data of non-progressive patients' image-review from a prospective randomized phase II trial of amrubicin as single agent or in combination with cisplatin versus etoposide cisplatin as first-line treatment [17]. Of 71 patients, 13 patients presented new osteoblastic lesions but simultaneously had a good response in the primary-disease-site or in the extraosseous sites, so the new bone-lesions were considered as an osteoblastic reaction of previously unrecognized bone-lesions. For bone metastases detection in SCLC, bone scintigraphy was routinely used as the method of choice, but it had a well-known limited sensitivity for osteolytic metastases, whereas MRI is regarded as the most sensitive method to detect bone metastases. In recent years, several studies demonstrated that 18-FDG-PET might improve and simplify staging, with a superior detection rate of bone metastases than bone scintigraphy. MRI and PET reveal bone or bone marrow replacement in up to 70% of patients with SCLC at initial presentation, whereas bone scintigraphy misses 30-60% of cases and CT probably even more [5,18,19]. A more extended use of 18-FDG-PET for baseline staging would likely lead to a greater finding of bone involvement at diagnosis. Furthermore, the improvement in overall survival with the new standard of care (first-line chemo-immunotherapy) in patients with ES-SCLC, could lead to a greater finding of osteoblastic healings, as a possible expression of treatment efficacy. Here we present five cases of osteoblastic response following the administration chemo-immunotherapy for ES-SCLC. Patients developed osteoblastic lesions seen on CT-scan with a simultaneous disease response to ongoing treatment on other sites. Only one patient had known 18-FDG-PET positive but CT negative bone-metastases before starting treatment. Although pathologic confirmation of tumour free lesion was obtained for only one patient, in any case the osteoblastic lesions, developed during therapy, were considered likely to be an osteoblastic response reflecting bone repair and treatment efficacy. Despite the appearance of the lesions, four patients remained completely asymptomatic. Instead, the woman presented a worsening back-pain following an acute vertebral collapse related to osteoporosis.

In conclusion, as different patterns of response, especially in case of bone lesions modifications, could lead to potential blunders for radiologists and clinical oncologists, is important to remember that osteoblastic bone response does not always mean disease progression, mostly in case of visceral disease

remission. With the increasing use of chemo-immunotherapy, tumour flare as radiological finding may have higher incidence and it is important to recognize it correctly, aiming to avoid early treatment discontinuation also given the lack of effective second-line treatment.

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