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Title:

A rare case report: an inextricable shoulder pain as the exclusive presentation of lung adenocarcinoma with metastasis over contralateral clavicle

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Structured Abstract

Background:

Lung cancer is the fourth most common form of tumor spreading to the bone. Among all patients of the lung carcinoma, the most common sites of bone metastasis are vertebrae, ribs, and pelvis. By comparison, the clavicle is an extremely rare site of metastases in not only the population of lung cancers but among all type of tumors. Enlightened by this existing fact, we would like to share our experience of management of an uncommon clavicular metastasis and illuminate the obscure mechanism of its scarcity.

Case presentation:

A 56-year-old female without any preknown systemic disease had suffered from a sole intermittent right shoulder pain without any other discomfort for 3 months. Physical examination performed at our orthopedic department showed tenderness over right distal third of clavicle with limited range-of-motion of right shoulder. EGFR-mutated lung adenocarcinoma with metastasis over right clavicle resulting in a pathological fracture was diagnosed according to the result of incisional biopsy. Concurrent chemoradiation therapy accompanied with target therapy was performed. Eighteen months postoperatively, the clavicle pain was found to be subsided with stationary bony lesion under appropriate medication and palliative radiotherapy during the subsequent follow-up.

Conclusions:

The clavicle is an exceedingly unusual site with 2% of metastatic involvement of all type of tumors and only 1% among the population of carcinoma of lung due to its scanty red marrow and sparse vascular supply. Despite unpleasant prognosis of clavicular metastasis from primary lung adenocarcinoma, promising quality of life is achievable under multidisciplinary management.

Keywords

Clavicular metastasis; lung adenocarcinoma; sites of metastasis

Background

Lung carcinoma is the fourth most common form of tumor (about 30~40%) spreading to the bone, behind breast(65~75%), prostate(65~75%) and thyroid cancer(about 60%)^[1]. Among the patients of lung carcinoma, the most common metastatic sites are vertebrae, ribs, and pelvis^[2]. By comparison, the clavicle is an extremely rare site of metastasis not only in lung cancer but of all types of tumors with only 1~2% involvement^[3,4,5]. Owing to its scarcity, there is no firm guideline of the treatment among this population. With the consent of the patient, we herein present a case of lung adenocarcinoma located at left upper lobe, who suffered from a right clavicular metastasis, for discussing the reason of its rarity and sharing our experience of management.

Case presentation

A 56-year-old female without any preknown systemic disease presenting with an isolated intermittent right shoulder pain, especially at night, for about three months visited our orthopedic department for help. During the past three months, rheumatoid arthritis of right shoulder was initially diagnosed and had been treated with medication at the other hospital, but in vain. Upon the physical examination at our department, tenderness over right distal third of clavicle accompanied with limited range-of-motion of right shoulder were observed. Plain radiograph of right clavicle showed osteolytic moth-eaten appearance with osteosclerotic periosteal reaction^[Fig.1]. Bone metastasis or osteomyelitis were firstly impressed. Subsequent whole-body bone scan revealed an intense linear uptake with osteosclerotic change over right clavicle and an osteolytic lesion with focal hot spot over cervical vertebra^[Fig.2]. Thus, she was admitted to our ward for further evaluation and management.

After admission, we performed a list of work-up for tumor. Blood analysis showed elevated carcinoembryonic antigen(CEA) level without any other abnormality. Computed tomography(CT) of chest demonstrated a 4.4cm mass over left upper lobe(LUL) of lung with miliary nodules over bilateral lungs and enlarged lymph nodes over bilateral hilar and left lower paratracheal regions^[Fig.3]. Heterogeneous bone density with fracture and adjacent soft tissue lesion was observed over right clavicle with an osteolytic lesion over vertebral body of C5^[Fig.4.5]. Lung cancer of LUL with bilateral lung metastasis and bone metastasis, staged cT4N3M1c according to AJCC 8th edition of cancer staging, was diagnosed. Magnetic resonance imaging(MRI) disclosed a consistent result of an infiltrative mass lesion(9.3cm*4.5cm*3.3cm) with deconstruction of bone, transcortical and extraosseous soft tissue invasion arising from right clavicle^[Fig.6]. With consent of patient, incisional biopsy of right clavicular lesion and CT-guided biopsy of tumor over LUL were performed step by step. After operation, she had a stable postoperative course and was soon discharged home. The specimen of the lesion over right clavicle disclosed a microscopical picture of metastatic carcinoma with tumor cells immunohistochemically positive for TTF-1 and negative for p40, which was compatible with the results of stains of primary EGFR-mutated lung adenocarcinoma. MRI of brain showed no imaging evidence of brain metastasis. Under the diagnosis of lung adenocarcinoma with bone metastasis, we conducted a series of multidisciplinary treatment for her. For treatment of EGFR-mutated advanced non-small cell lung carcinoma(NSCLC), gefitinib(250mg) was prescribed once a day. As for the bone metastasis, palliative radiotherapy(RT), total dose of 30Gy in 10 fractions over right clavicle and C5 in the period of 2 weeks, was administered with subcutaneous injection of denosumab(120mg) once a month. In the past one year postoperatively, right clavicular pain had been gradually subsided under the treatment of local RT and the usage of denosumab. Following whole-body bone scan showed partial resolution of previous intense uptake over right clavicle and C5 with post-treatment response^[Fig.7]. Follow-up of chest CT disclosed a progressively reduced size of tumor over LUL and stationary lesion over right clavicle, indicating partial response of target therapy. In

comparison with the radiograph performed at the admission, the latest image presented focal sclerotic change of right clavicle with obviously increased bone density^[Fig.8]. Under multidisciplinary management of orthopedist, pulmonologist, and radiation oncologist, her clinical condition is now stationary without further progression. Regular outpatient follow-up will be arranged for closely monitoring the primary lung cancer and metastatic bone lesion.

Discussion

Lung carcinoma is the fourth most common form of tumor (about 30~40%) spreading to the bone, behind breast (65~75%), prostate (65~75%) and thyroid cancer (about 60%)^[1]. Bone has been reported to be the second most common distant metastatic site of lung cancer (34%) and the most common one of NSCLC (34.3%)^[6,7]. However, traced back to the published literature, researchers declared the clavicle to be an exceedingly rare site of metastasis not only in lung cancer but of all types of tumor^[3,4,5]. Thai DM et al. reported a retrospective analysis of 93 cases with 95 sites of bone metastasis to humerus and shoulder girdle. There were only 2 cases of clavicular metastasis among 93 patients of all types of tumor^[3]. Sugiura H et al. retrospectively reviewed 118 cases of lung cancer with 318 sites of bone metastasis, in which the incidence of metastasis to vertebra (42%), ribs (20%), and pelvis (18%) accounted for the majority. Metastases to clavicle was reported to occur in only 1% of patients^[4]. Tsuya A et al. demonstrated a retrospective investigation of 70 cases of non-small cell lung carcinoma accompanied with bone metastasis, which revealed a familiar result of dominant metastasis to vertebra (50.0%) and rib (27.1%). There was even no case of clavicular metastasis reported in this population^[5]. On the basis of published literature, the clavicle was considered to be a rare site of metastasis, which occurred in our case. This existing fact enlightened us to search for the obscure mechanism of the scarcity of this site of metastasis.

Metastasis is a series of processes including dissociation from primary tumor, cell migration, access to systemic circulation, escape of immunosurveillance, and eventually growing at the distant organs^[8]. Bone metastasis, or to be precisely, bone marrow metastasis, is facilitated by the fenestrated structure of the red marrow sinusoid capillaries for transvascular migration of the tumor cells from the nutrient artery to the bone marrow and adhesive factors on tumor cell for adhesion to the stromal cells as well as the bone matrix. By disruption of the bone homeostasis, disseminated tumor cells in the bone marrow progressively covert the normal niches in to metastatic lesions after overcoming immunosurveillance^[9]. Owing to the characteristic mechanism, abundant amount of hematopoietically active red bone marrow and high blood perfusion of the metastatic area indeed play an indispensable role in the process of metastasis. The distribution of red bone marrow and the sufficiency of its blood supply perfectly demonstrated the reason of why axial bones are much more commonly involved rather than the appendicular bones^[4,8,9,10].

Clavicle is seemed to meet the nature of insufficient red marrow and blood supply, which contributed to its rarity of metastasis. In terms of the blood perfusion, FW Knudsen et al. declared

three tiny branches of subclavian artery including suprascapular artery, clavicular branch of thoracoacromial artery, and the internal thoracic artery to be the primarily periosteal blood supply of the clavicle. No nutrient artery was observed^[11]. Lack of its own main nutrient artery, the clavicle, unlike the most of other long bones, does not have adequate medullary cavity to store the red bone marrow for nurturing the circulating tumor cells. As mentioned above, apart from the blood supply, the amount of hematopoietically active red bone marrow in the clavicle is relatively scanty to build a suitable niche for metastasis. In 1980s, M Cristy et al. published an analysis of calculating the regional distribution of active bone marrow at various ages via multiple methods of previous studies. Among all bones in our bodies, the percentage of active red marrow in the clavicle is the most impoverished one, with merely 0.7~1.0% at each stage of age^[12]. In 2000s, PF Caracappa et al. conducted an analysis of two methods of calculating red bone marrow mass via the radiation dose of computed tomography. Through these two methods, the calculated masses of red bone marrow in the clavicle are the second to last among whole body, with only 16.7 grams and 11.0 grams respectively^[13]. By comparison, in these two studies mentioned above, the bellwether of incidence of bone metastasis such as vertebra, rib, and pelvic all play the leading roles in not merely the percentage but the actual weight of red bone marrow as well^[12.13]. The result coincidentally corresponds the observation of review of Sugiura H et al. that high concentration of red bone marrow positively correlates to high incidence of bone metastasis^[4]. As for the management of the clavicular metastasis, palliative radiotherapy including single 8Gy fraction and multiple fraction regimens such as 30Gy in 10 fractions, are recommended for pain relief and maintain or ameliorate skeletal function^[14.15]. Denosumab, a human monoclonal antibody that specifically binds to receptor activator of NF- κ B ligand which regulates the bone modeling, provided a tremendous impact on delaying the time of first skeletal-related event and presented a promising overall survival, time to disease progression and safety profile^[16.17]. For its unpleasant outcome, improvement of quality of life should be the given priority for any therapeutic approaches in the management of bone metastasis.

Conclusions

With its sparse vascular supply and scanty red marrow, the clavicle is an extremely rare site with only 2% of metastatic involvement of all type of tumors^[3.18]. Although the exceedingly low incidence of clavicular metastasis of primary lung adenocarcinoma foretells an unfortunate short-term median survival^[19], the patient's quality of life can be significantly improved with a favorable prognosis under a multidisciplinary management.

List of abbreviations

1. Carcinoembryonic antigen(CEA)
2. Computed tomography(CT)
3. Left upper lobe(LUL)

4. Magnetic resonance imaging(MRI)
5. Non-small cell lung carcinoma(NSCLC)
6. Radiotherapy(RT)

Declarations

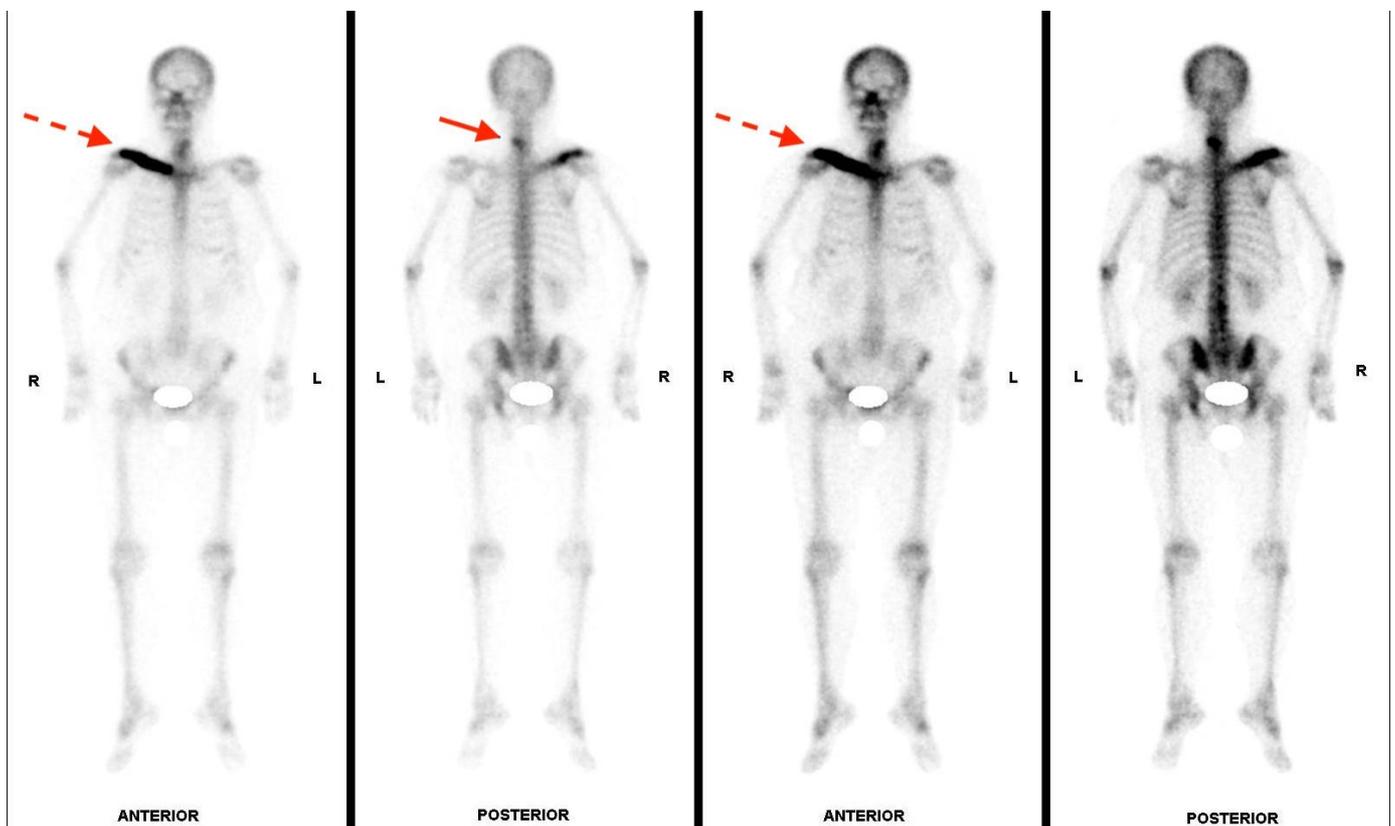
1. **Ethics approval and consent to participate:** not applicable
2. **Consent for publication:** Written informed consent for publication of their clinical details and clinical images was obtained from the patient.
3. **Availability of data and materials:** not applicable
4. **Competing interests:** The authors declare that they have no competing interests.
5. **Funding:** not applicable
6. **Authors' contributions:**
Karl Wu- conceived the case report and revised the manuscript
Yu-Hao Huang- drafted the manuscript
7. **Acknowledgements:** not applicable

Figure

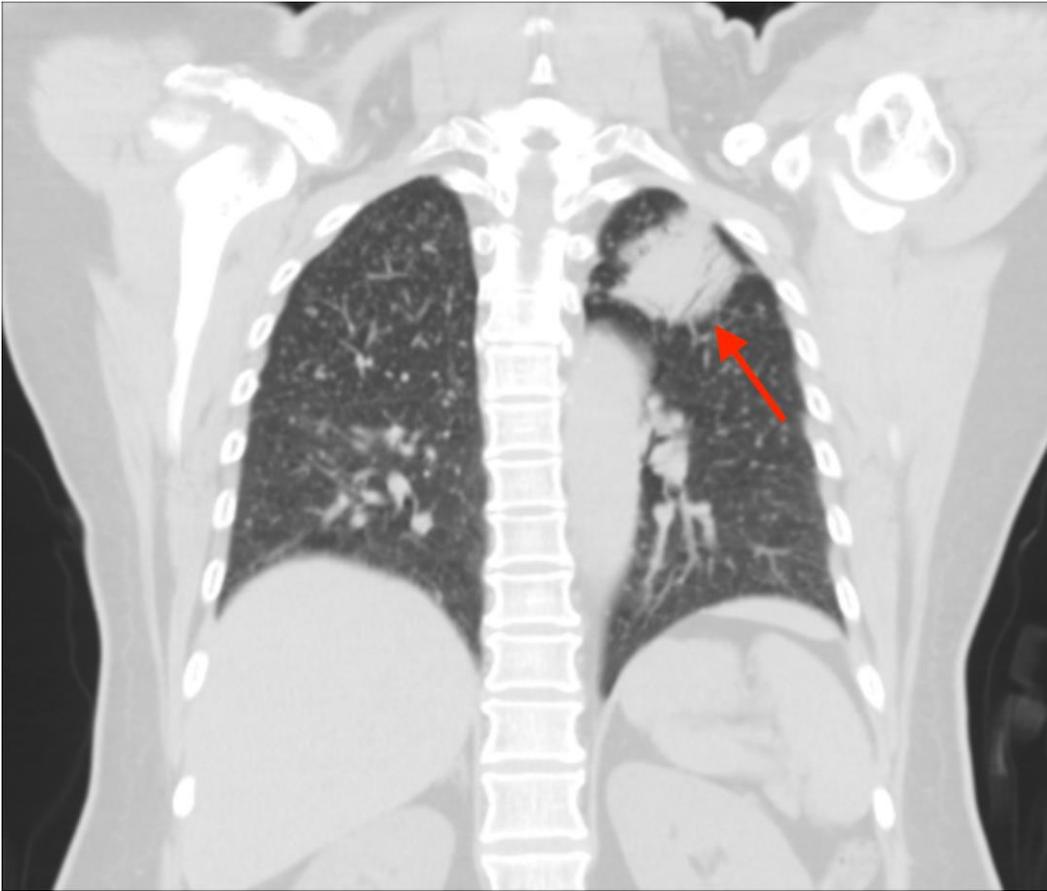
[Fig.1] Plain radiograph of the right clavicle showed osteolytic moth-eaten appearance with osteosclerotic periosteal reaction.



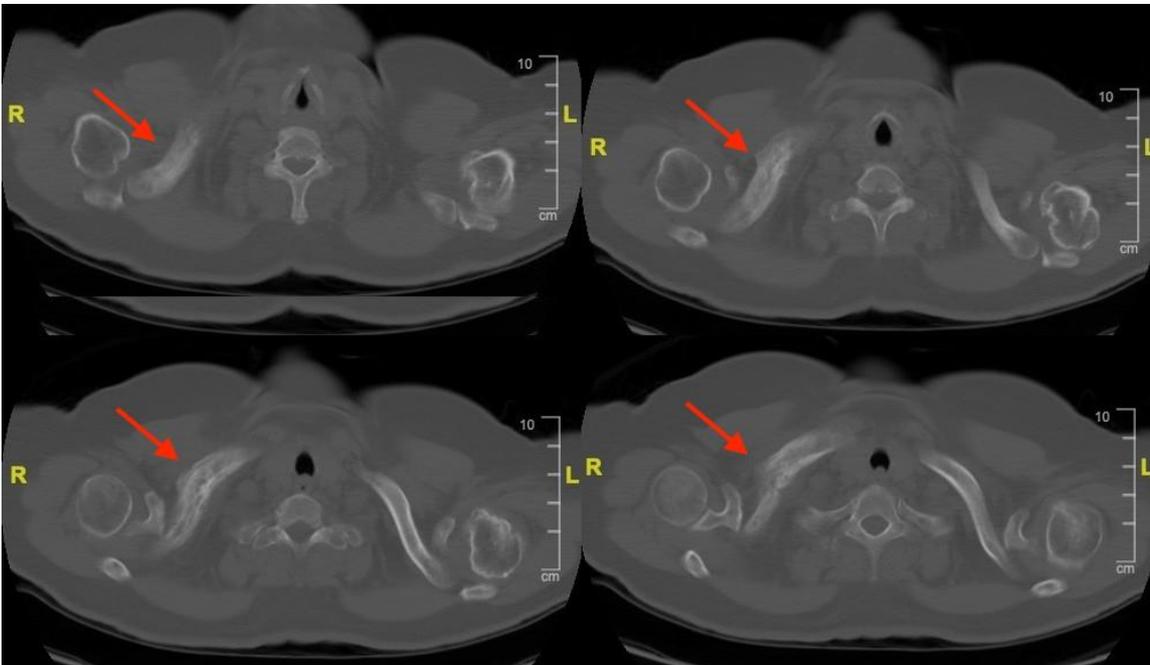
[Fig.2] Whole-body bone scan revealed an intense linear uptake in right clavicle and a focal hot spot in cervical spine. (Solid arrow: cervical vertebra; Dotted arrow: right clavicle)



[Fig.3] CT of chest in lung window demonstrated a 4.4cm mass(arrow) located at LUL of lung.



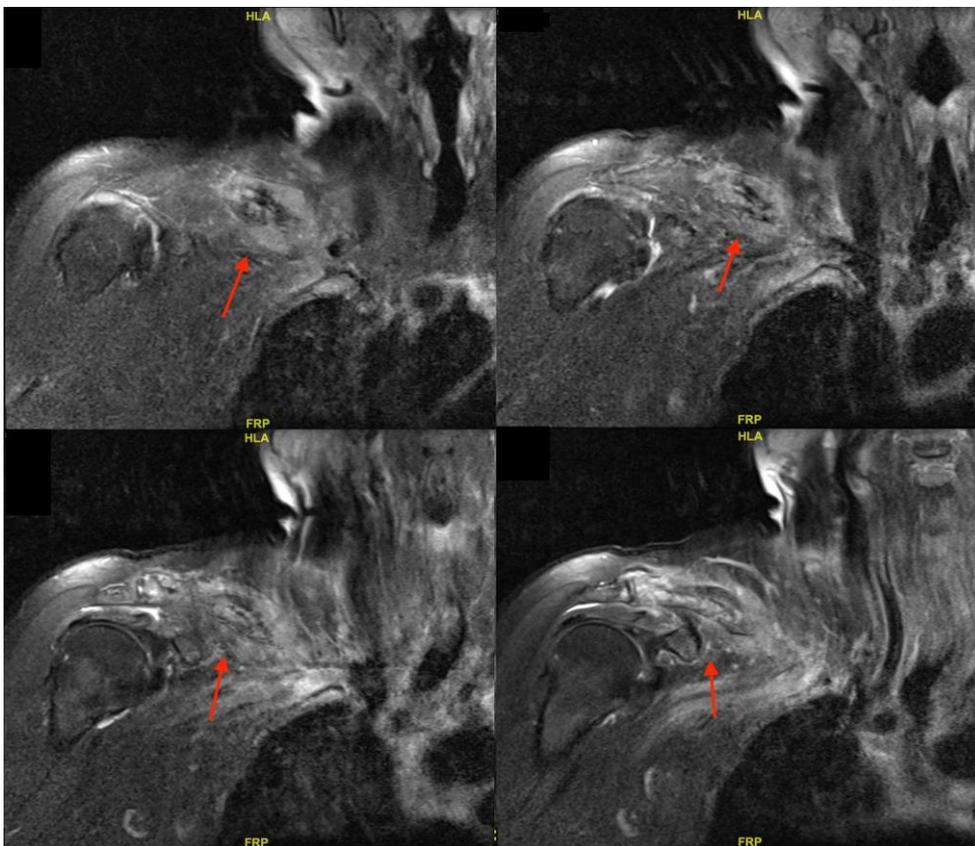
[Fig.4] CT of chest in bone window disclosed heterogenous bone density with fracture and adjacent soft tissue lesion of right clavicle. (Arrows: clavicle lesion)



[Fig.5] An osteolytic lesion(arrow) was observed over vertebral body of C5.

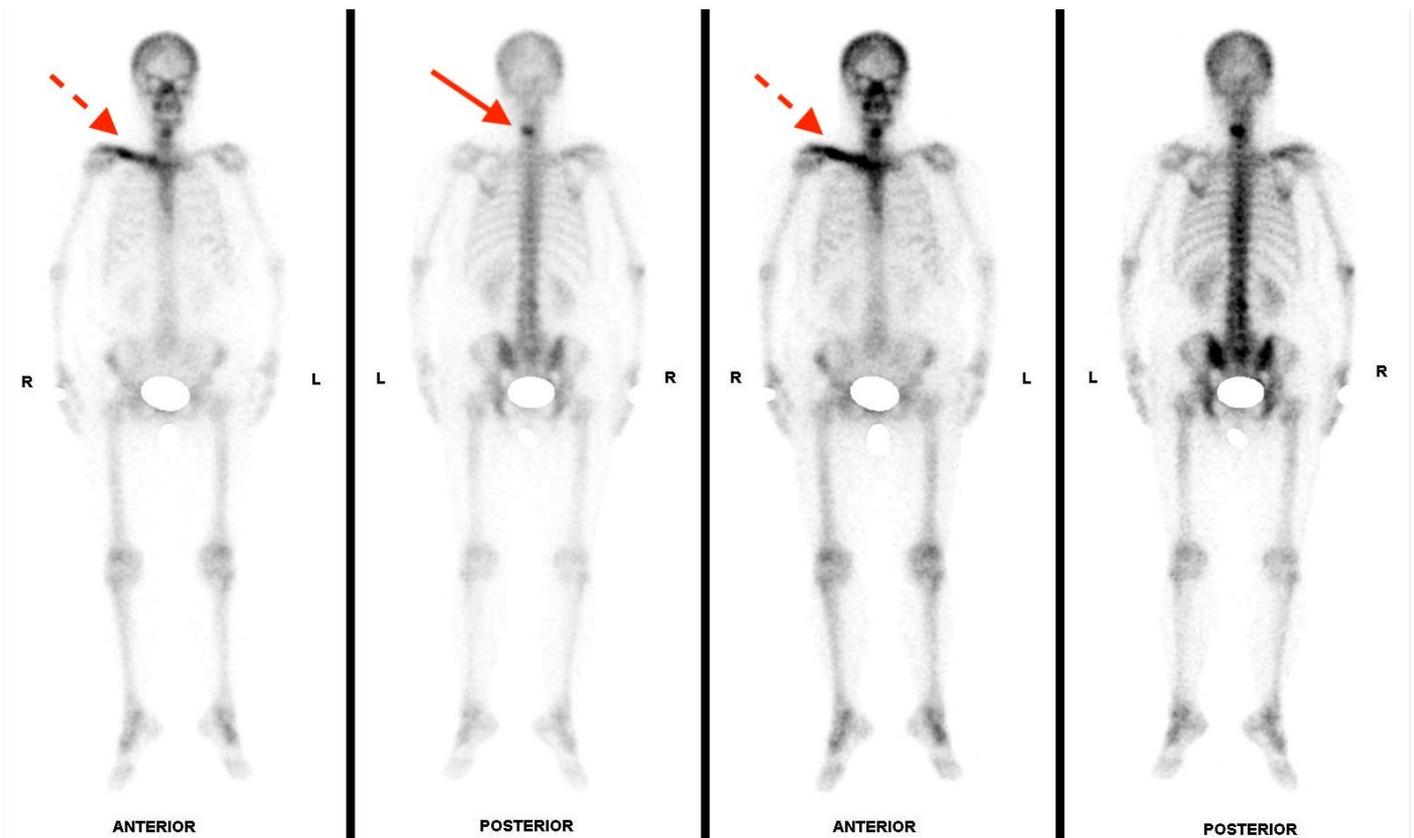


[Fig.6] Magnetic resonance imaging(MRI) of right shoulder presented with a consistent result of an infiltrative mass lesion(9.3cm*4.5cm*3.3cm, arrows) with deconstruction of bone.



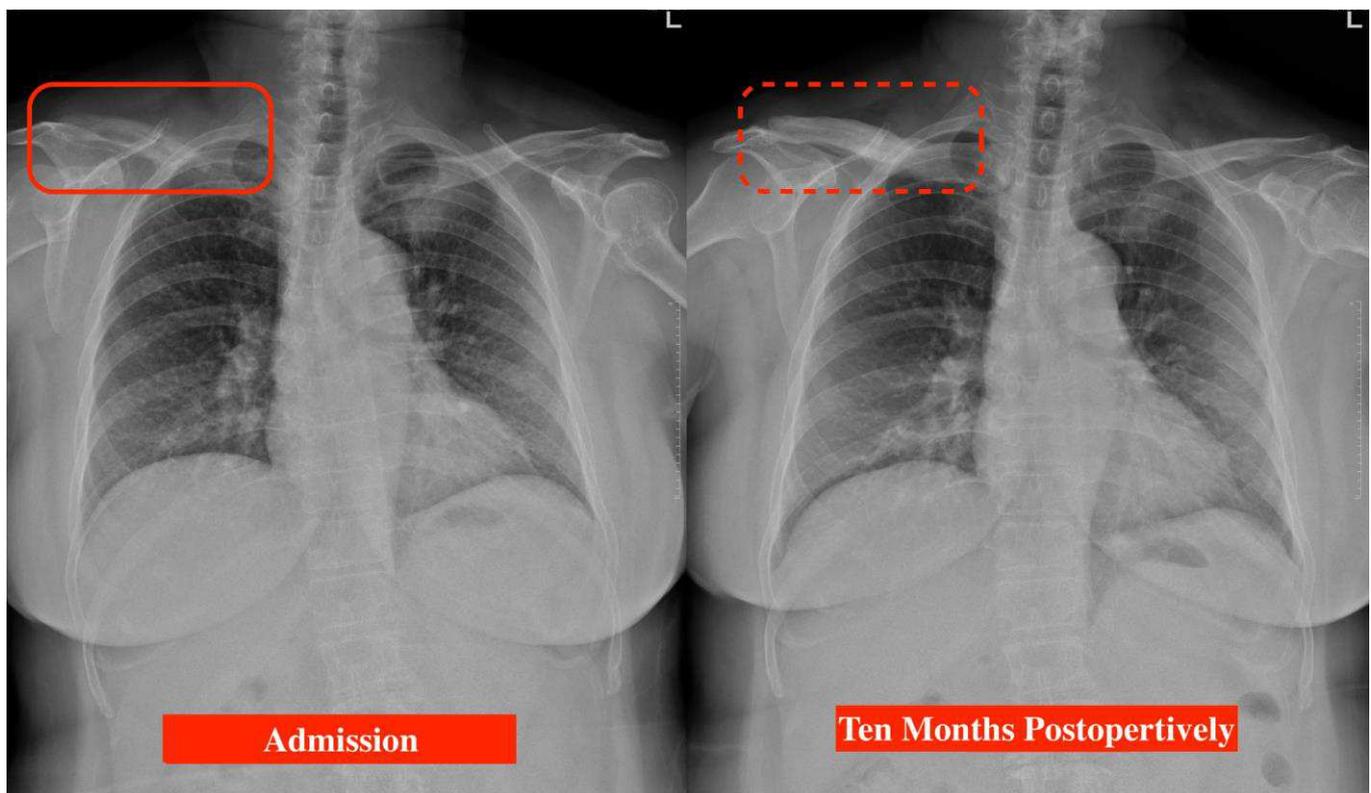
[Fig.7] Four months postoperatively, whole-body bone scan revealed partial resolution of previous intense uptake over right clavicle and C5 with post-treatment response.

(Solid arrow: cervical vertebra; Dotted arrow: right clavicle)



[Fig.8] In comparison with the chest x-ray performed at the admission, the latest image presented with focal sclerotic change of right clavicle with obviously increased bone density.

(Solid frame: admission; Dotted frame: the latest follow-up, ten-months postoperatively)



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Figures

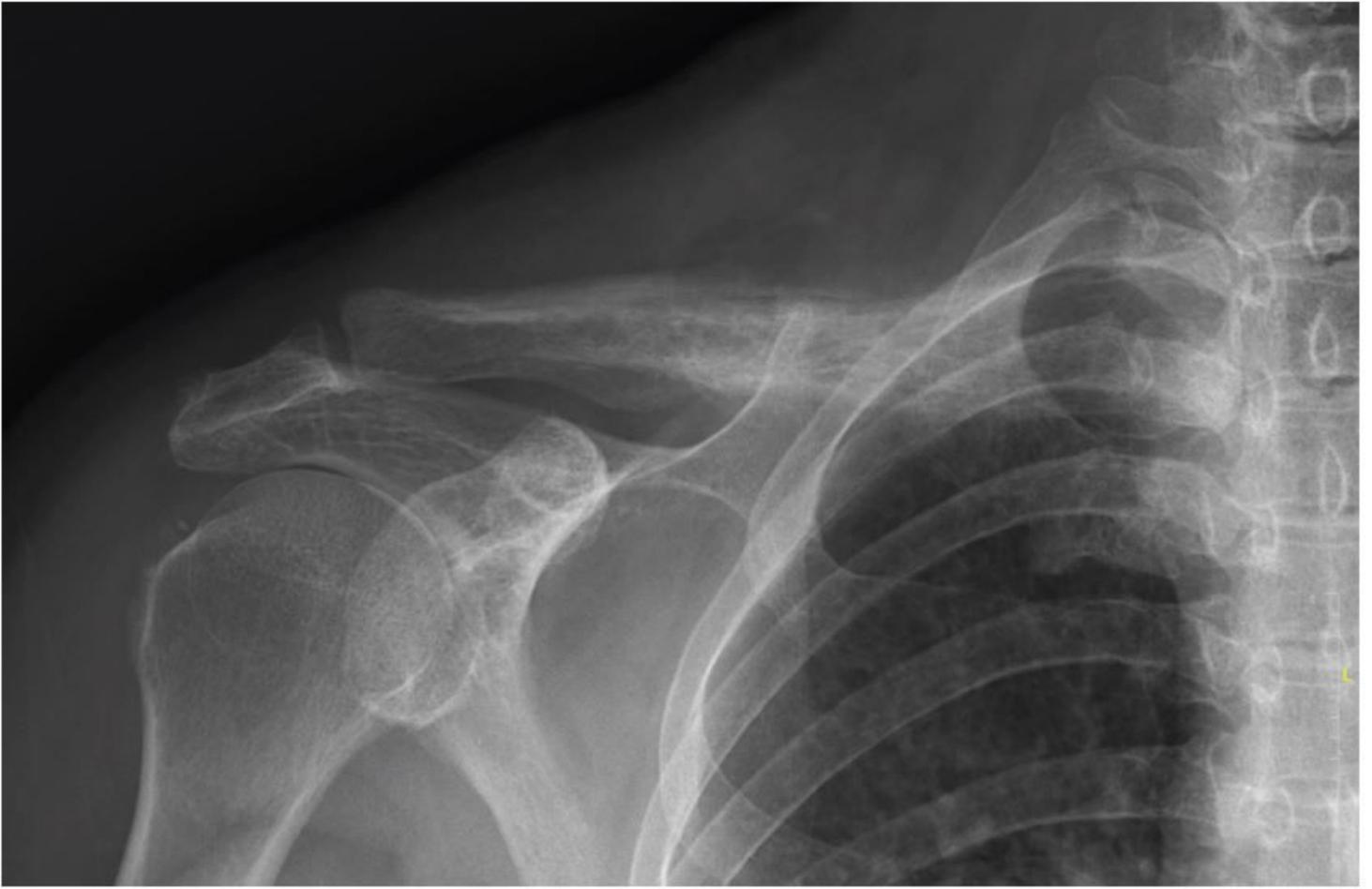


Figure 1

Plain radiograph of the right clavicle showed osteolytic moth-eaten appearance with osteosclerotic periosteal reaction.

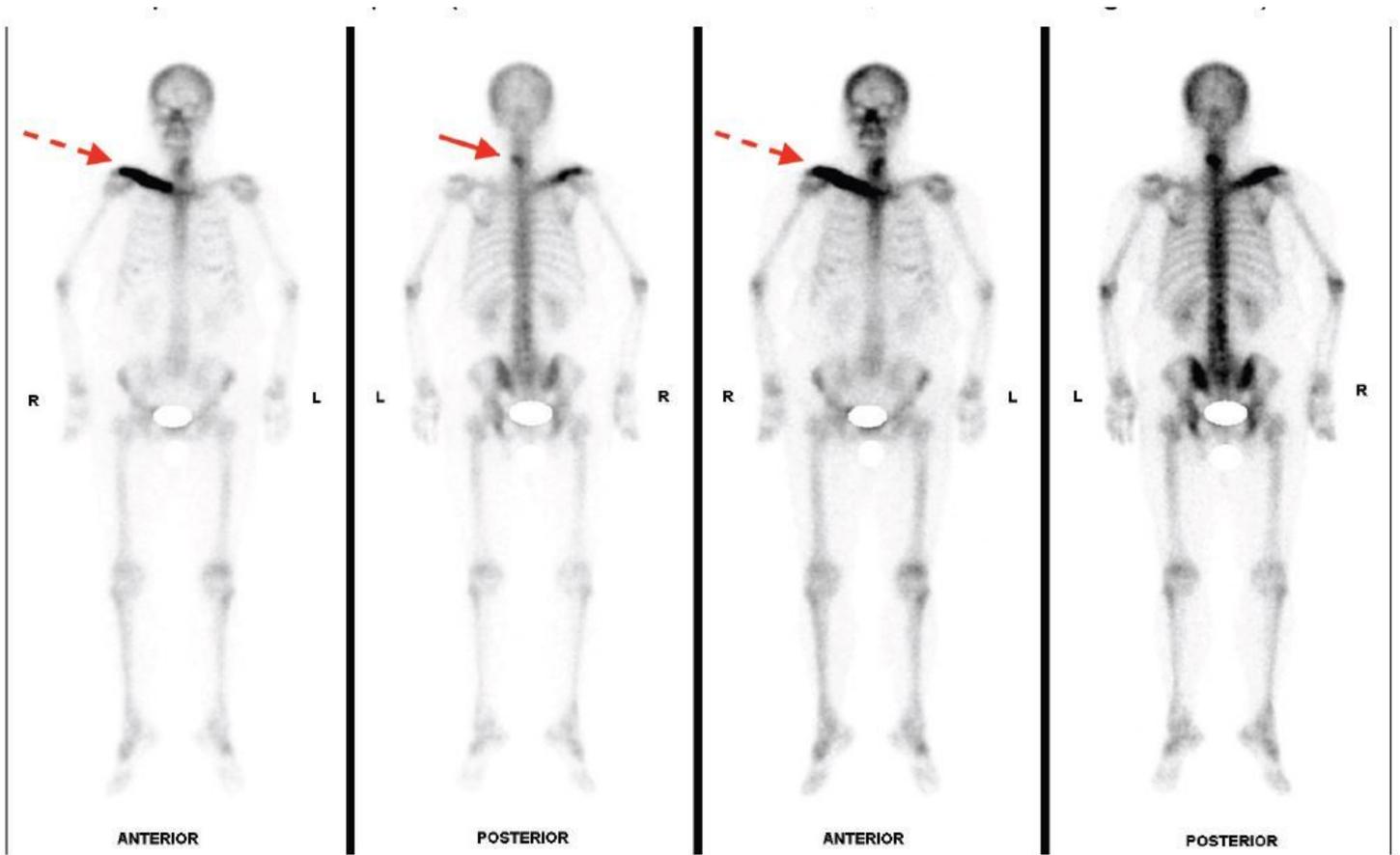


Figure 2

Whole-body bone scan revealed an intense linear uptake in right clavicle and a focal hot spot in cervical spine. (Solid arrow: cervical vertebra; Dotted arrow: right clavicle)

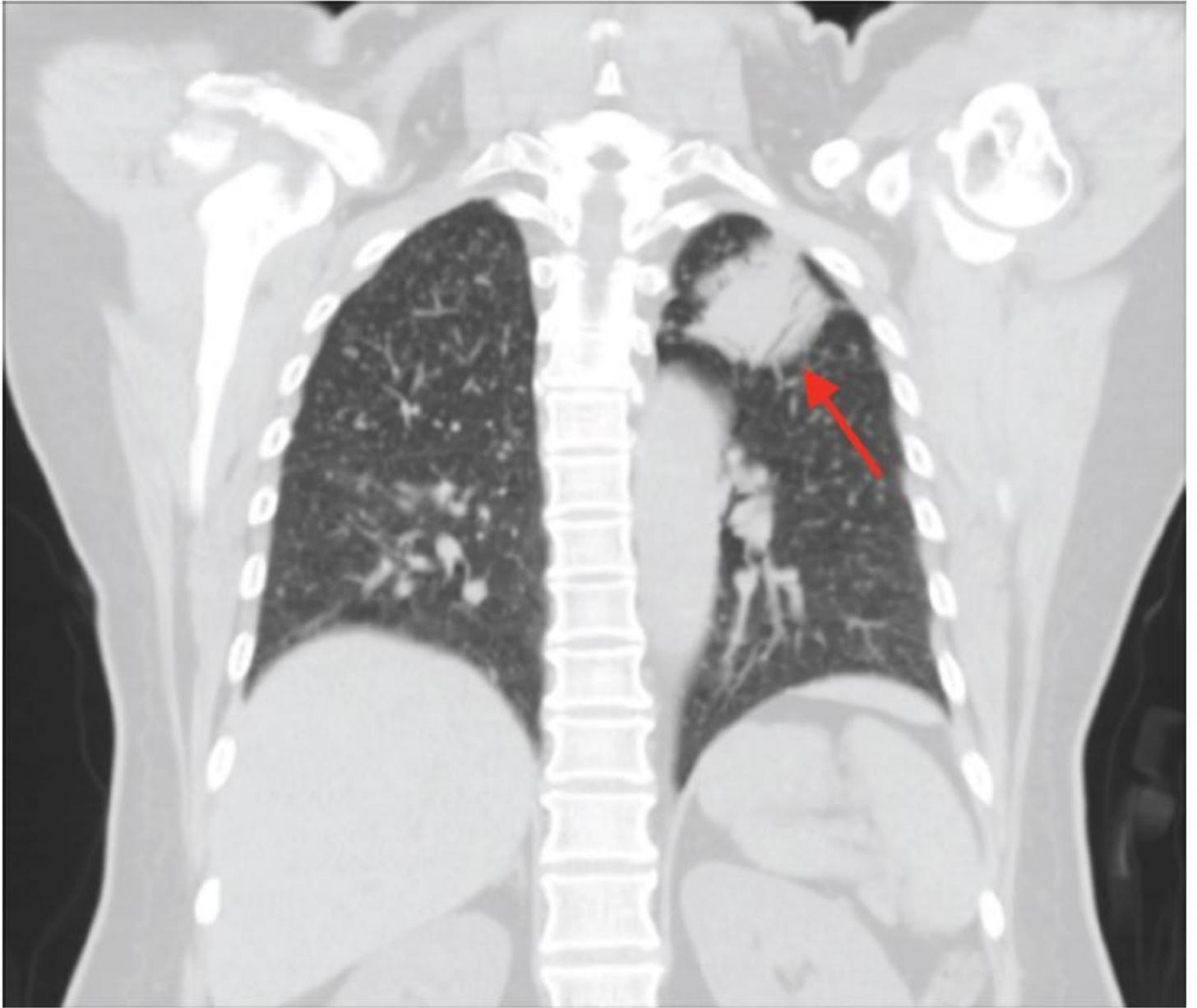


Figure 3

CT of chest in lung window demonstrated a 4.4cm mass(arrow) located at LUL of lung.

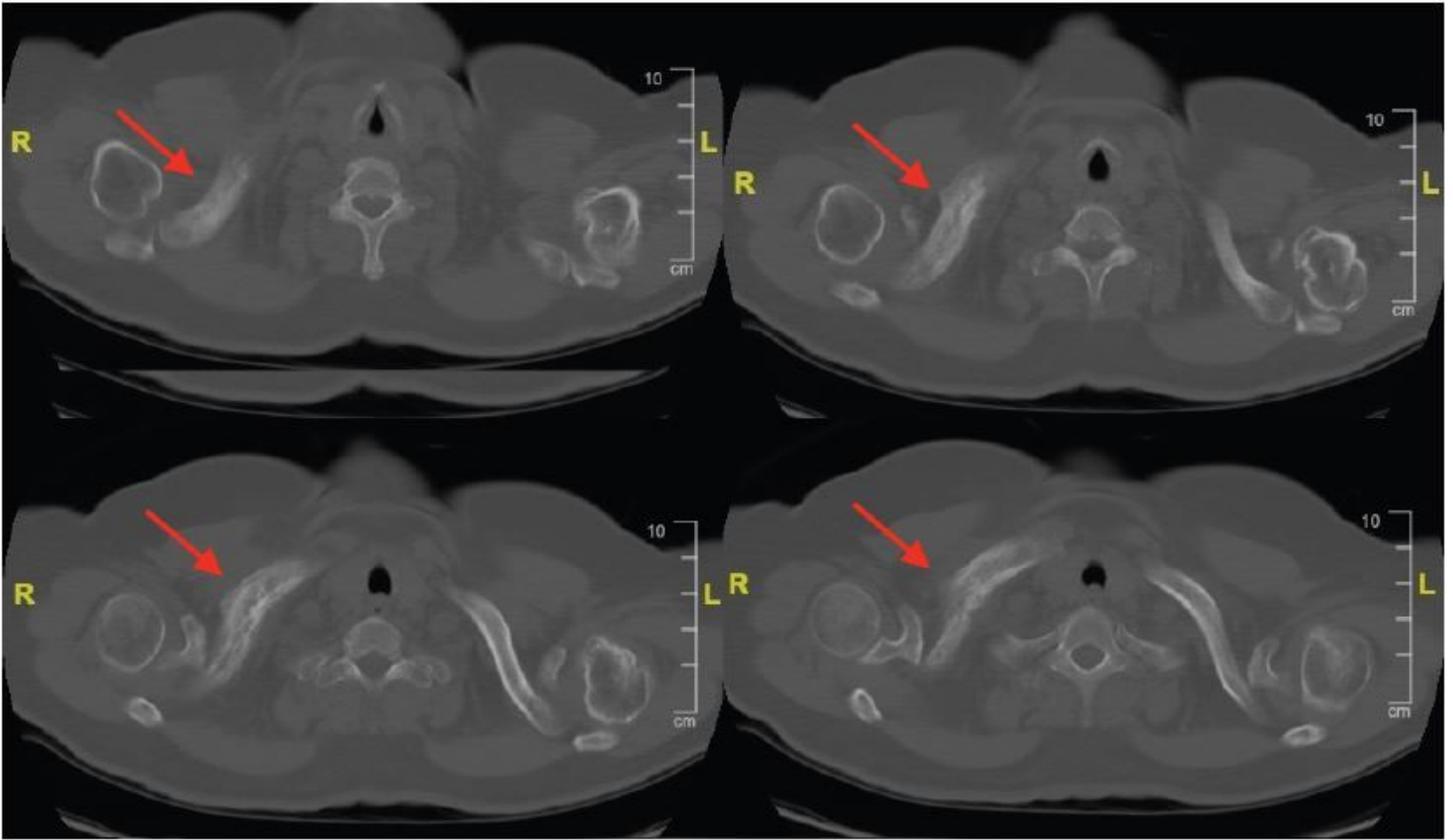


Figure 4

CT of chest in bone window disclosed heterogenous bone density with fracture and adjacent soft tissue lesion of right clavicle. (Arrows: clavicle lesion)

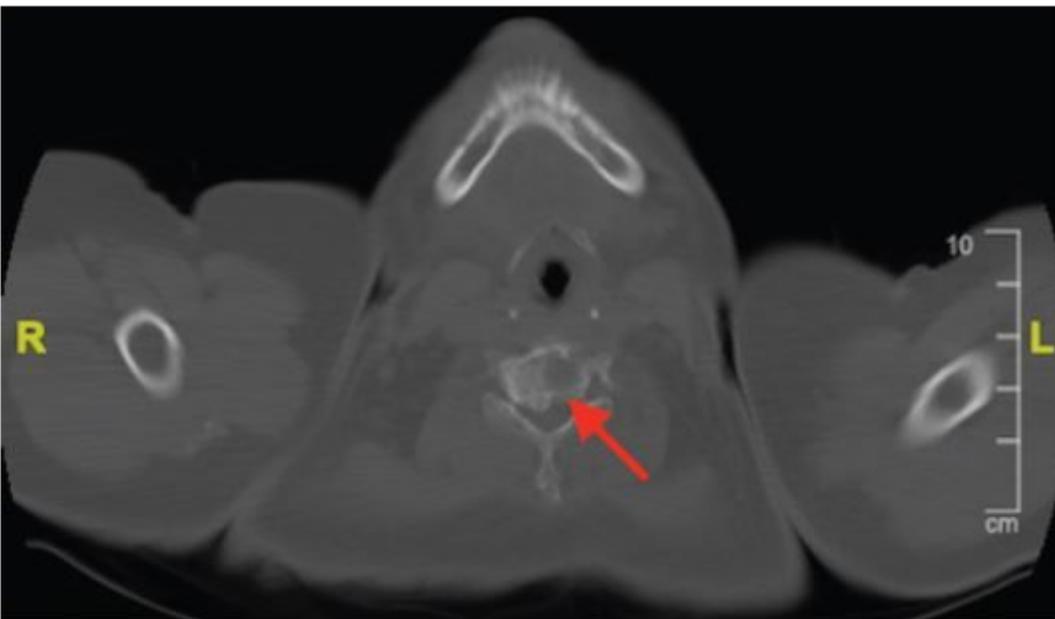


Figure 5

An osteolytic lesion(arrow) was observed over vertebral body of C5.

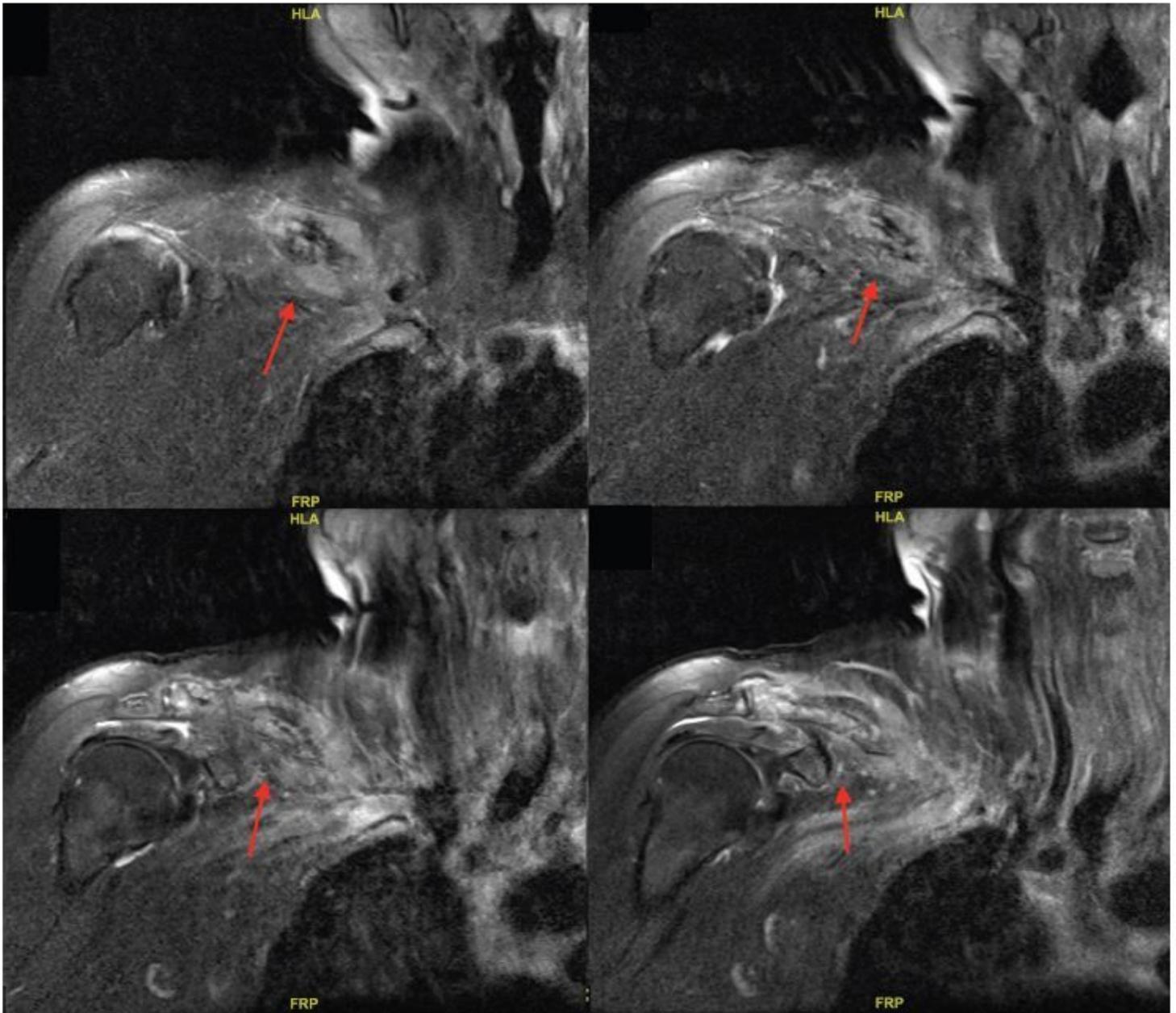


Figure 6

Magnetic resonance imaging(MRI) of right shoulder presented with a consistent result of an infiltrative mass lesion(9.3cm*4.5cm*3.3cm, arrows) with deconstruction of bone.

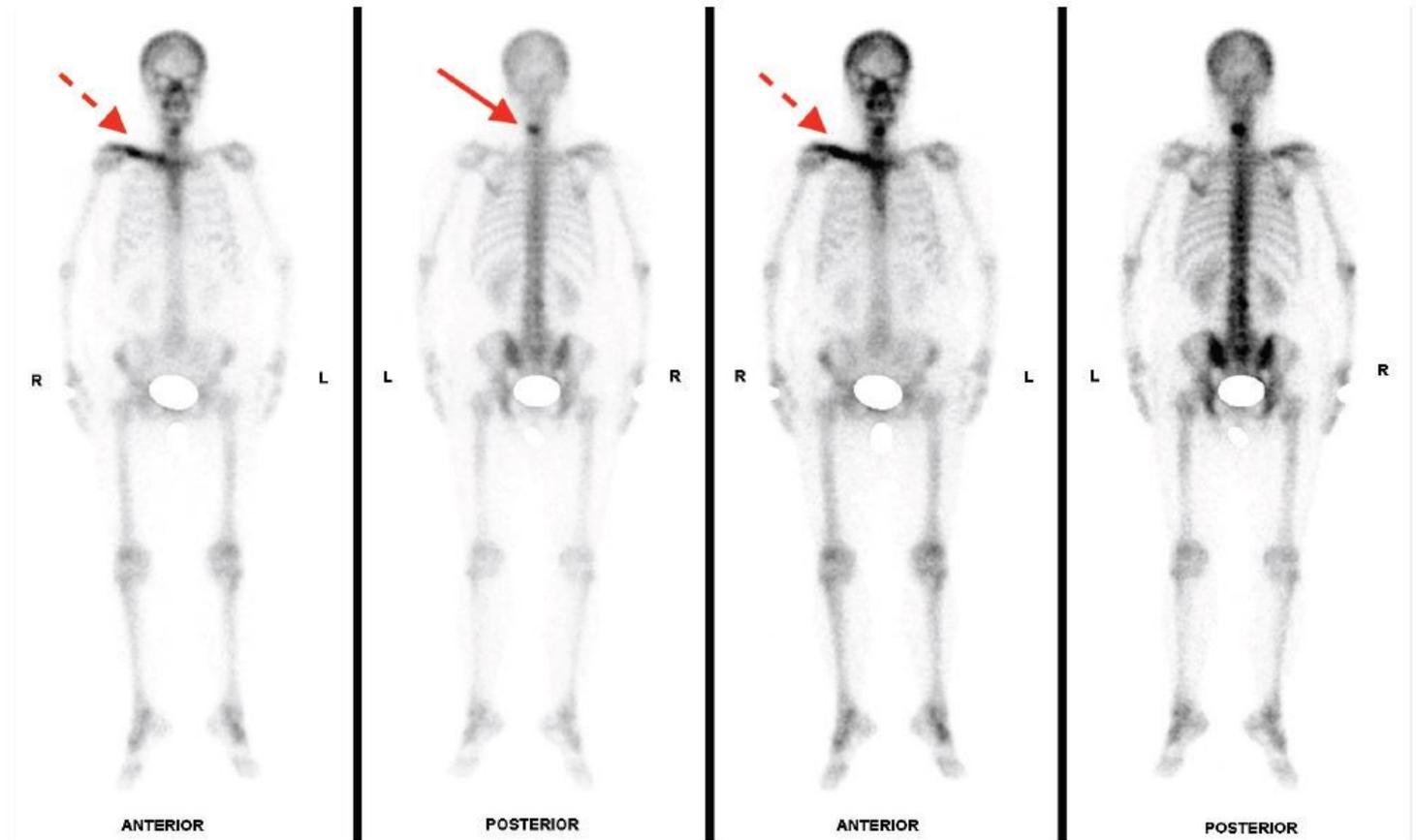


Figure 7

Four months postoperatively, whole-body bone scan revealed partial resolution of previous intense uptake over right clavicle and C5 with post-treatment response. (Solid arrow: cervical vertebra; Dotted arrow: right clavicle)

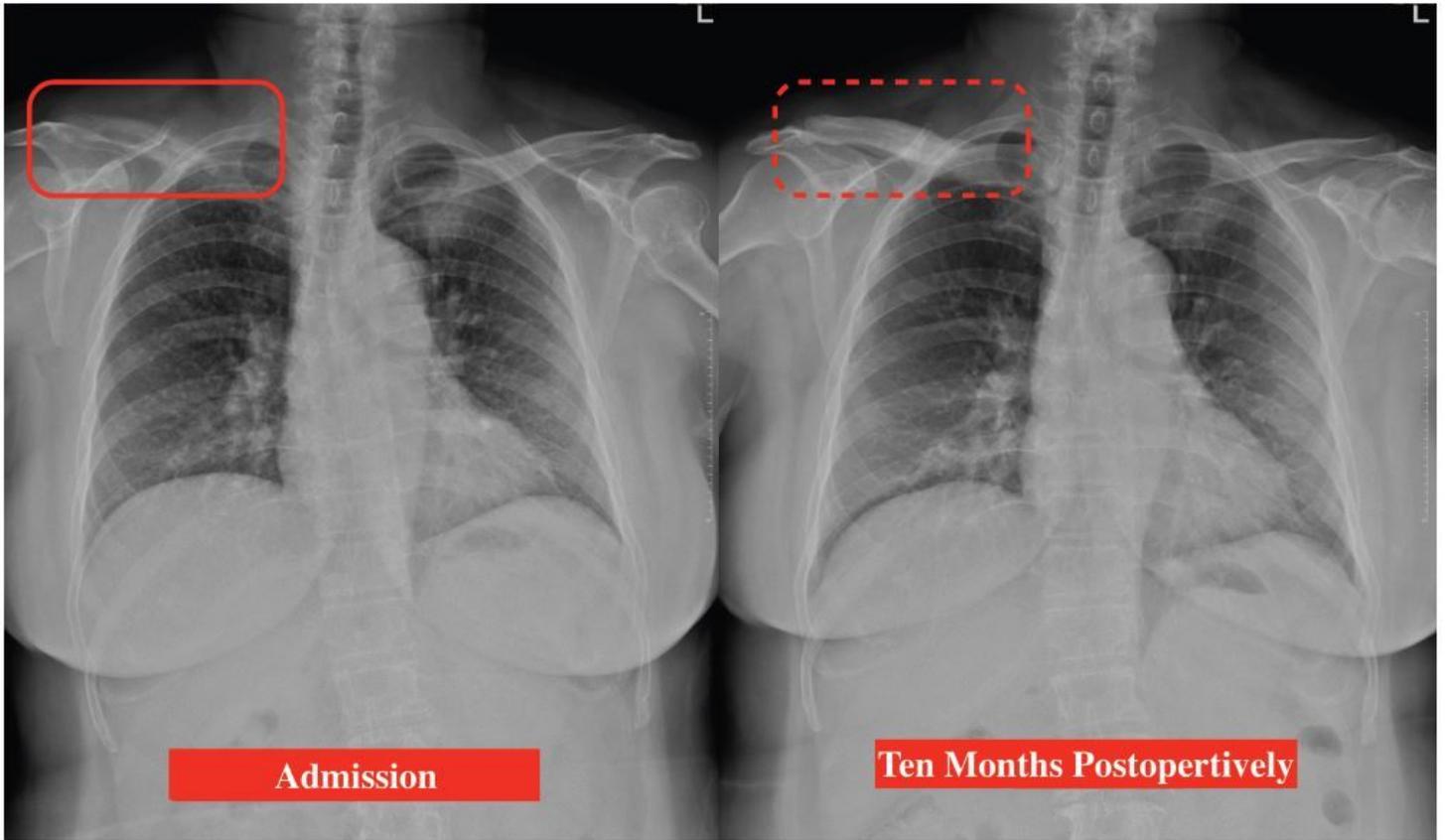


Figure 8

In comparison with the chest x-ray performed at the admission, the latest image presented with focal sclerotic change of right clavicle with obviously increased bone density. (Solid frame: admission; Dotted frame: the latest follow-up, ten-months postoperatively)