

Unusual jaw metastasis from squamous cell lung cancer in heavy smoker

Two case reports and review of the literature

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Abstract

Rationale: Jaw metastasis is a very rare condition associated with lung cancer evolution. In this paper we present two cases of patients who underwent different approach.

Lung cancer is the leading cause of cancer related death worldwide. Survival depends on the staging and biology of tumor. Smoking may affect the prognosis.

Patient concerns: There are herein reported the cases of two patients affected by squamous cell lung cancer with spread to mandibular bone.

Diagnoses: In the first case a computed tomography (CT scan) showed a large mass located in upper right lung, then bronchoscopy was performed with biopsies and the histology revealed a squamous cell carcinoma P63+ and TTF-. In the second case upper right lung mass with metastases to mediastinal bilateral lymph nodes was found at CT scan. A bronchial biopsy revealed a squamous cell carcinoma p63 positive and TTF-1 negative.

Interventions: The first, a 65-years old man, current heavy smoker who quit and relapsed, at initial stage of IIa (T2aN1M0), after initial neo-adjuvant chemotherapy underwent lung lobectomy and lymph nodes resection. Three months later a metastasis located on mandibular bone was found out. The second case, a 68-years old female heavy smoker, at initial stage IIIb not available for surgery because of involvement of bilateral lymph nodes, underwent first line course chemotherapy with cisplatin and vinorelbine and second line with erlotinib.

Outcomes: The first patient underwent hyperthermia and radiotherapy but a sepsis developed and patients died. In the second case, after two months from the beginning of II line the patient developed a jaw metastasis and underwent surgery with resection of hemi-mandible, but soon after she died because of pulmonary embolism.

Lessons: These cases highlight the poor prognosis of patients current smokers affected by squamous cell lung cancer. The jaw bone localization is very rare and different approach could be applied.

Abbreviations: COPD = chronic obstructive pulmonary disease, CT = computed tomography, FEV1 = 1 second forced expiratory volume, MPK = mitogen-activated protein kinase, MRI = magnetic resonance imaging.

Keywords: different approach, heavy smoking, jaw metastasis, squamous cell lung carcinoma

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1. Introduction

Lung cancer is the main cause of cancer-related death worldwide.^[1] The incidence is increasing, representing 12% of new cases of cancer disease,^[1] and the mortality is roughly about 90%. The most frequent sites of metastases are liver, bone, brain, and pleura.^[2] The jaw metastasis has been very seldom found out in lung cancer patients. We want to point out the aggressiveness and the atypical course of the disease in presence of comorbidities, despite the use of all necessary therapeutic tools. We want also to highlight the possibility of different therapeutic approaches to the metastatic site.

2. Case report 1

In January 2014, a 65-year-old patient came to our observation in outpatient settings owing to exertional and at rest dyspnea along with chest pain. He was a current smoker (40 pack-years) and reported significant passive smoke exposure in childhood.



Figure 1. (A) Computed tomography (CT) scan showing a huge mass sited in upper right lung. (B) Chest x-ray check after lobectomy showing absence of disease. (C) MRI showing mass infiltrating the ascending branch of jaw bone. MRI = magnetic resonance imaging.

Physical examination showed decreased breath sounds with prolonged expiration notably in the right side of the chest. The main comorbidity was hypertension along with chronic obstructive pulmonary disease (COPD).

At lung examination, crackles were present in lower lobes and whistles, and groans were present in right hemi-thorax.

Among blood tests, white blood cell count was $11 \times 10^3/\mu\text{L}$ with 80% of neutrophils, hemoglobin 13.8 g/L, protein chain reaction 5 mg/L, and carcinoembryonic antigen level 7.2 ng/mL.

Spirometry revealed a 1 second forced expiratory volume (FEV1) of 48% of predicted and FEV1/forced expiratory capacity 66%, outlining a framework of severe COPD according to global initiative for chronic obstructive lung disease guidelines.^[3]

Hemogas analysis of arterial blood sample showed pH 7.43, PaCO₂ 47 mm Hg, PaO₂ 55 mm Hg, HCO₃ 31.2 mmol/L, carboxyhemoglobin (COHb) 3.1%, exhaled CO 12 ppm, which expresses a smoking habit.

The computed tomography (CT) scan showed a large mass located in upper right lung (Fig. 1A), infiltrating the main right bronchus with hilar lymph adenopathies. A bronchoscopy was performed with biopsies. The histology revealed a squamous cell carcinoma P63+ and TTF-. Hence, the patient underwent lung resection by lobectomy and removal of local lymph nodes. The initial staging according to TNM staging system was T2aN1M0 because of peri-bronchial lymph nodes involvement and the main lesion longest diameter of 3.5 cm.^[4]

Subsequently, the patient began a chemotherapy with cisplatin 80 mg/m² and vinorelbine 30 mg/m² d 1, 8, 21 for 4 courses.

At the following chest x-ray, the finding was an absence of the disease (Fig. 1B). Moreover, through counseling and nicotine replacement therapy, the patient quit smoking.

Owing to a blood toxicity (anemia and neutropenia grade III) and in presence of stable disease, the therapy was shifted to erlotinib, an epithelial growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), which is available for second-line therapy in squamous cell carcinoma or after first-line therapy four courses irrespective of gene mutation, according to the literature.^[5] In the meantime, the patient resumed smoking documented by detection of exhaled CO 15 ppm.

Three months later, a jaw metastasis located at the ascending branch was observed clinically and by magnetic resonance imaging (MRI) (Fig. 1C).

The patient no longer had the possibility to eat and underwent nutritional support therapy.

The lesion had been treated with radiotherapy total dose of 40 Gy fractionated in 2 Gy per day, along with hyperthermia. The

latter was practiced through a radiofrequency heating device with maximum output at 800 W. The treatment was well tolerated and improved symptoms such as pain, but he developed a massive pulmonary embolism with associated acute lung failure. The patient died few weeks later. Before death, signed informed consent of the relatives was obtained for the case publication.

3. Case report 2

In December 2014, a 65-year-old female heavy smoker with pack-years above 40, presented to our clinic because of chest pain and exertional dyspnea.

The patient had a previous breast resection because of carcinoma in her health history.

An initial radiological evaluation showed an upper right lung mass with metastases to mediastinal bilateral lymph nodes. A bronchial biopsy revealed a squamous cell carcinoma p63+ and TTF1-.

The patient began a treatment with cisplatin 80 mg/m² and vinorelbine 25 mg/m² d 1, 8, 21 for 4 courses. After an initial response, the patient reported recurrence and she started a therapy with erlotinib 100 mg/d. After two months from the second course a mass involving the right mandibular bone was found. An intraoral examination appreciated a huge ulcerating lesion easily bleeding of the mandibular bone, total mobility of dental elements. The patient complained with spontaneous pain resistant to any treatment. She underwent a CT of facial skeleton (Fig. 2 A and B) and orthopantomography (Fig. 2C and D). Given the pathological fracture, the bleeding, and strong pain, it was decided that the patient be submitted to mandibular resection surgery. The patient therefore underwent hemimandible resection. Given the poor prognosis and the palliative purpose, reconstruction of tissue was not performed. It was positioned drainage and performed a check by orthopantomography again.

The patient died 7 days after surgery as a result of bleeding and embolism at hospital ward.

4. Discussion

Two cases of lung cancer spread to an unusual site are herein reported.

Different stages have shared the same outcome. A different approach to mandible bone metastasis was undertaken.

The stage of disease determines the rate of survival,^[5] dropping down from 70% of stage I to 2% of stage IV. In nonsmall cell

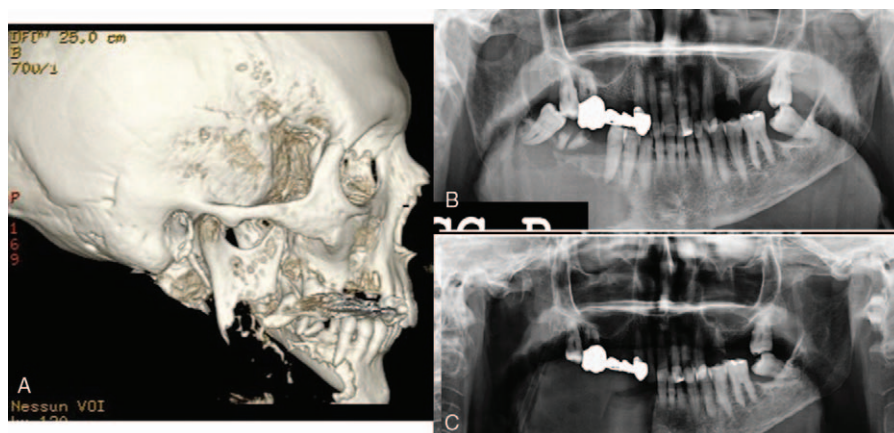


Figure 2. (A) Computed tomography (CT) 3D highlighting the involvement of the entire right hemi-mandible with bone erosion of the body and part of the mandibular branch. (B) CT in axial projection highlighting a huge mass involving the bone, and also the soft tissue. (C) Ortho-panoramic radiography highlighting the outcome of complete resection of right hemi-mandible.

lung cancer patients who undergo lung resection, the best approach after surgery is adjuvant therapy with drugs such as cisplatin and vinorelbine to lengthen the survival.^[6] Despite the use of chemotherapy after surgery and subsequent second-line therapy, the disease spread to the jaw. In the first case the local treatment by radiotherapy and hyperthermia became ineffective with respect to survival. We suppose that the resumption of smoking habit fostered the unresponsiveness of tumor to treatment and the unusual spread of tumor cells. Indeed, smoke compounds could induce chemo-resistance by several pathways, bringing about an altered metabolism of drugs and inducing uncontrolled cell proliferation.^[7,8]

The spread of disease to the bone is found in over 30% of patients affected by lung cancer.^[7]

The jaw location is very rare,^[9] and most of the time, it is presented like a metastatic disease.

Going into depth, in the first case, we want to point out that the perseverance in smoking habit could induce a quick evolution of the disease favoring unusual spread.^[10,11] The metastases from lung cancer out of the usual sites were very rarely described; 1 case of metastasis to bulbus oculi and maxillary sinus was reported by Ates et al.^[11,12] Indeed, it has been demonstrated that tobacco smoking contains more than 4000 assessed substances, gases, and particulate are detrimental, alike. In particular, those substances are able to activate cytochrome P450 that in turn activates pro-carcinogenic agents such as nitrosamine compounds. Moreover, smoke cigarette agents such as polycyclic hydrocarbons interfere with drug metabolism by inducing cytochrome P450 2A6 and 1A1.^[8,10] Therefore, the effectiveness of therapy is also compromised through biological and genetic factors. One of the drugs affected in its activity by smoking habit is erlotinib, an anti-EGFR. On the contrary, smoking cessation showed potential benefits in patients with COPD at risk for lung cancer suggesting a link between the 2 illnesses.^[11]

The squamous cell histotype represents 20% of all types and is not suitable to new drugs acting as anti-EGFR, with the exception of erlotinib, owing to a low incidence of EGFR mutation. This drug was approved as second-line therapy according to the study BR21 showing a benefit in terms of progression-free survival.^[13] Notwithstanding, it is not enough to achieve a good control of the disease as shown in the present report. The use of hyperthermia along with radiotherapy, having the aim to achieve a good

control of pain by determining a minimal tumor temperature higher than 43°C, should be considered for the improvement of symptoms.^[14]

In the second case, the surgery approach to mandible bone metastasis was decided because of symptoms as a palliative therapy. The initial stage was more advanced than the first case, but the outcome was similar. We assume that in both cases, the persistence of smoking status has affected the outcome by interfering with drugs and fostering and unusual spread of the illness.^[8,15]

Indeed, smoking habit through its compounds could bring about lung cancer initiation and progression. In particular, nicotine and its nitrosamine derivatives promote in addition to activation of oncogens, the expression of some proteins such as adhesion molecules and vascular growth factor, fostering the dissemination of disease. Tumor growth and progression are also induced by nicotine receptor stimulation and following downstream activation of signaling cascade such as mitogen-activated protein kinase (MAPK) in turn promoting cell proliferation.^[8] On the contrary, cigarette smoke compounds are a powerful enzymatic inducer through its activity on cytochrome P450 2A6, which has been found associated with high lung cancer incidence in animal model.^[15] Going into depth, smoking could also interfere with anticancer drug metabolism, inducing, for example, cisplatin resistance through activation of Bcl-2 protein and TKI resistance through plasma level reduction of the aforementioned drug and its protein-mediated inactivation.^[15]

When the illness becomes metastatic, the purpose of clinicians should be to improve quality of life.

5. Conclusions

We hypothesize that aggressiveness of disease probably caused the abnormal spread of the tumor. Though this assertion is supported from only 2 cases, we observed that similar outcome was reached from patients affected by the same cancer type and having in common the insistence in smoking habit. The recurrence of smoking habit, and also the presence of COPD could worsen the outcome and it can hinder the effectiveness of treatment.

The initial stage of disease did not ensure a benign prognosis. The use of hyperthermia along with radiotherapy is a good

practice in local metastases, but not enough to lengthen survival. Conversely, surgery is an option to choose in case of heavy symptoms, and bleeding but it is at risk for complications as we found in the case herein reported.

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