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Mandibular metastasis of pulmonary adenocarcinoma: How unexpected could it be?

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Objective: Metastatic tumours of bone must be considered in all patients with unexplained bone pain and particularly in patients who present with a known cancer, localised pain at multiple sites, and radiographic findings suggestive of metastasis. The purpose of this report was to present a case of a pathological fracture of the mandible as a consequence of metastatic pulmonary adenocarcinoma.

Materials and Methods: In July 2018 a 68-year-old male patient was hospitalised because of pulmonary adenocarcinoma and attended our department for an oral maxillo-facial evaluation. He complained of pain and swelling in the right temporo-mandibular region resulting in a reported functional limitation.

An Orthopantomogram (OPG) demonstrated a right intracapsular condylar compound fracture associated with an osteolytic lesion at the condyle base with jagged margins. Subsequently, a CT scan with contrast of the maxillo-facial complex and a fine-needle aspiration of the lesion was performed.

Results: CT images showed the presence of a right mandibular condyle fracture associated with a large osteolytic lesion which confirmed the pathological nature of the fracture. Fine-needle aspiration of the lesion confirmed its metastatic nature. It was not possible to proceed with a mandibular resection due to the critical clinical condition of the patient who died in September 2018.

Conclusion: Lung cancer frequently produces lytic-type metastasis, sometimes even in the jaw. In patients with an established diagnosis of lung cancer, any radiolucent lesion of the jaw or an unexplained painful symptomatology to the oro-maxillo facial complex should be placed in differential diagnosis with metastasis of the primary tumour.

KEYWORDS
lung adenocarcinoma, mandible, mandibular fracture, metastasis, pathologic fracture

1 | INTRODUCTION

Currently, lung cancer represents approximately 12% of worldwide new cancer diagnosis[1]; initially asymptomatic, it is often diagnosed at advanced stages, when patients have already developed metastatic disease.[2,3] Improvements in molecular pathology detection methods and targeted therapies have markedly increased the overall survival of patients with adenocarcinoma based on the emerging concept of "precision medicine" in recent years.[4] Even though there has been progress in the diagnosis and treatment of lung cancer, 5-year survival rates are still around 7%–15%.[5]

Lung cancer is a deadly disease and has two main subtypes: non-small-cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC); within them, lung adenocarcinoma is the most frequent subtype of NSCLC.[6,7,8] Previous studies have shown that lung adenocarcinoma patients have a shorter survival time than patients with another subtype of NSCLC.[9] In the 20th century, squamous cell carcinoma (SCC) was the most common histological subtype of primary lung cancer in men accounting for nearly half of all cases in the 1970s.[10] Since the 1980s, the relative frequency of SCC has declined with adenocarcinoma becoming the most common subtype by 1998–2002.[11] This shift has been attributed to several factors including: (1) the production of filtered cigarettes with lower tar content allowing deeper inhalation and more peripheral distribution of cigarette smoke, (2) increasing air pollution, and (3) earlier cessation of smoking. Adenocarcinoma is now the most common histological subtype of primary lung cancer accounting for greater than 40% of cases, and its relative frequency is increasing.[10–14]

In metastatic lung cancer, bone metastases are the most frequent followed by brain and liver[5]; the survival in patients with metastatic disease is reduced and, moreover, bone lesions can cause severe pain, pathological fractures, malignancy-related hypercalcemia and other complications that significantly negatively affect the quality of life.[15,16] In particular, metastatic diseases localised in the maxillo-facial region (jaw bones and soft tissues) are rare, comprising only up to 3% of oral cancer.[17] In order of frequency, primary tumours of the following organs can be found in the mandible: lung, breast, kidney, thyroid, liver, lower extremity, prostate, melanoma, colon-rectal, and uterus.[18] Kirschnick et al. put lung and breast cancer at the top of the list, followed by liver, thyroid, prostate, kidney and colon.[19] Metastases to the oral cavity may occur at any age but are most common during the fifth and sixth decades of life and the site of the primary tumour differs by gender.[18–20] In men, the most common primary site is the lung, followed by the kidney, prostate, liver, melanoma, and bones of the lower extremity, whereas in women it is the breast, followed by lungs, kidney, thyroid, female genital organs, and colon-rectum.[18,20] Concerning clinical signs, a mass, tumour or swelling were the most common, showing a male–female ratio of 2:1.[18] Young patients from 6 months to 17 years were more likely to have metastatic sarcomas with a better survival time after 5 to 10 years compared with adults.[18] In this paper, a case of a pathological fracture of a mandibular condyle caused by lung cancer metastasis has been described, with citations from the latest and most updated literature reviews.

2 | MATERIALS AND METHODS

Informed written consent was obtained from the patient to use data for the research that was conducted in agreement with the guidelines of the Helsinki Declaration as revised in 1975 and amended in October 2003.

A 68-year-old hospitalised patient was evaluated in the Unit of Maxillofacial Surgery and Stomatology (Ospedale Maggiore, Trieste, Italy) because of pain and functional limitation of the right temporomandibular region exacerbated in the previous few days. He rated pain as 5 on Numeric Rating Scale (NRS).[21] The medical history of the patient revealed that he had been previously hospitalised because of a lung adenocarcinoma diagnosed in November 2017 during a thoracic x-ray performed as preparation for liver surgery. In fact, an alteration of HBV markers was found in his blood in June of the same year, so the patient underwent a liver ultrasound which lead to the hypothesis of hepatocellular carcinoma. During preliminary exams performed before liver surgery, a lung mass was found in the right lung so further investigations carried on, revealing the presence of lung adenocarcinoma (T2-3 N2 Stage IIIA).

Carboplatin/Gemcitabine chemotherapy followed by radical radiotherapy associated with Cisplatin has been performed to treat primary lung pathology.

Concerning the maxillofacial region, extra oral examination revealed the presence of painful unilateral swelling in the right temporomandibular region although palpation of the temporomandibular joint (TMJ) did not lead to the perception of joint clicks a slight limitation of motion was observed with mouth opening. Intraorally, diffuse white lesions compatible with pseudomembranous candidiasis were detected.

An orthopanoramic X-ray (OPG) was performed and revealed the presence of a right mandibular condyle fracture associated with a large osteolytic lesion, located at the neck of the condyle (Figure 1); also, various dental problems were revealed by OPG such as periapical radiolucency in many mandibular teeth and long span bridgework with teeth and implants connected.

In agreement with the geriatrician who was treating the patient, a computed tomography (CT) of the maxillofacial complex was performed (Figures 2 and 3).

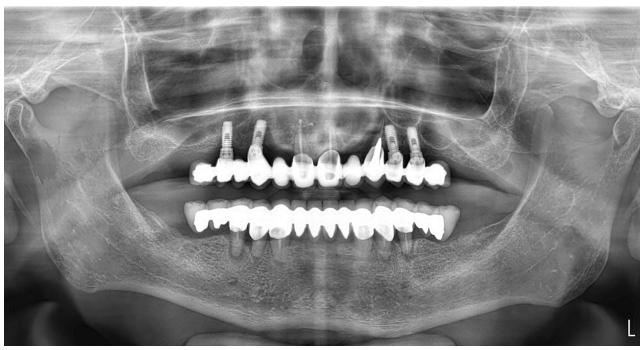

FIGURE 1 Orthopantomography

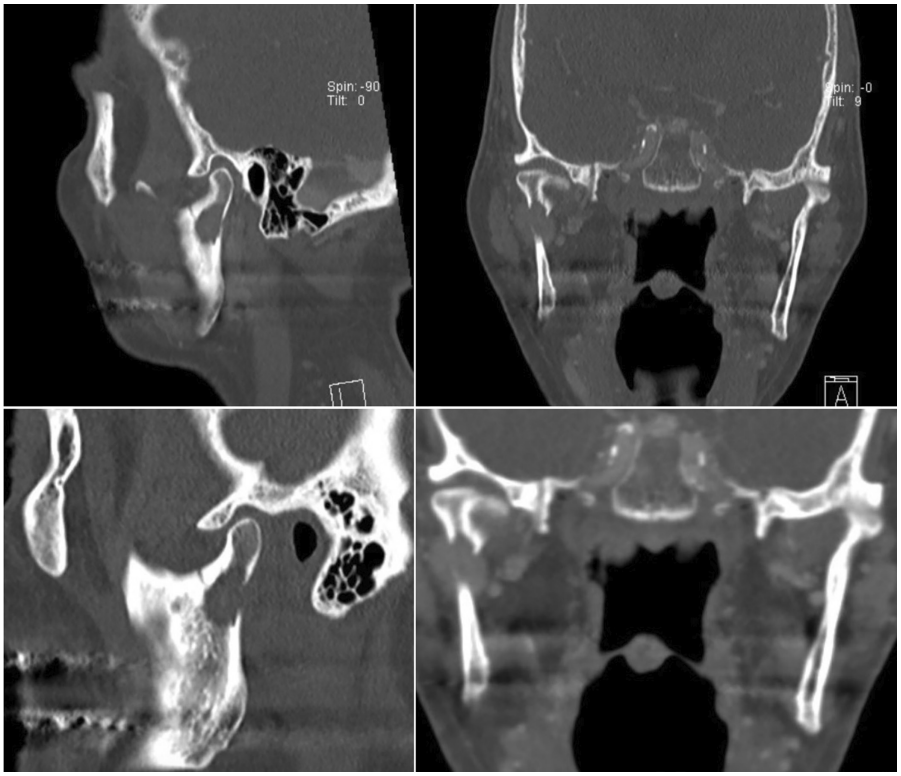

FIGURE 2 CT scan

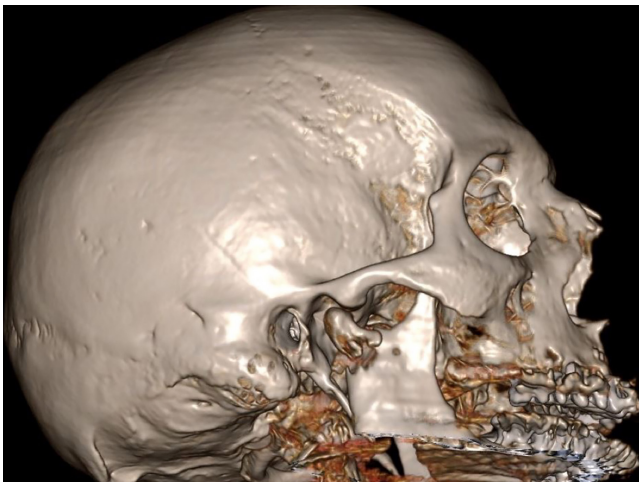

FIGURE 3 CT scan 3D reconstruction [Colour figure can be viewed at wileyonlinelibrary.com]

CT scan confirmed the presence of a right mandibular condyle fracture associated with a large osteolytic area, located at the neck of the condyle, whose size was approximately 9 mm anteroposteriorly, 6 mm medial-lateral, and 17 mm cranial-caudal. The lesion was characterised by irregular margins and cortical involvement both on the medial and lateral sides, which confirmed the pathological nature of the fracture. Suspicious lymphadenopathy was not observed in the cervical lymph nodes.

An ultrasound-guided fine needle biopsy was performed to investigate the condylar lesion and the cytologic analysis revealed the presence of medium and large-size adenocarcinoma cells with a large cytoplasm, sometimes apocrine in appearance with focal secreting aspects, mostly central nuclei with severe anisonucleosis and gross eosinophilic nucleoli (Figure 4).

In addition to the exams mentioned so far, total body scintigraphy was performed and focal accumulation of radiopharmaceutical in the humerus, spine, rib, femur and both mandibular condyles, mainly on the right one, revealed the presence of multiple bone lesions. A histologic examination after a spine biopsy, including lymph nodes, confirmed the metastatic nature of the lesions (Figure 5).

Collective discussion between maxillofacial surgeon and oncologist was performed to decide on a treatment plan for the patient; initially, maxillofacial surgery was considered the best way to proceed, but after 15 days, the patient's general condition was so poor that surgery was excluded and zoledronic acid therapy was proposed.

After a couple of months of the mandibular fracture, the patient died.

3 | DISCUSSION

The maxillofacial complex is an unusual site for metastasis, in fact, metastases to the entire maxillomandibular complex represent just 1% of metastatic disease and 1%–3% of all tumours in this area.[18,22] Bone metastases are considerably more common than the ones to soft tissues; the mandible, especially the body and condyles, are the

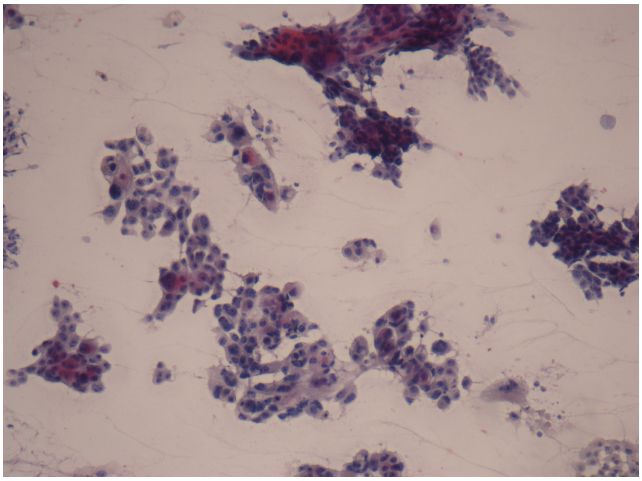

FIGURE 4 Aggregates of severely atypical cells. The large cytoplasm of apocrine type suggests an adenocarcinoma (c. 9876.18 HEx10) [Colour figure can be viewed at wileyonlinelibrary.com]

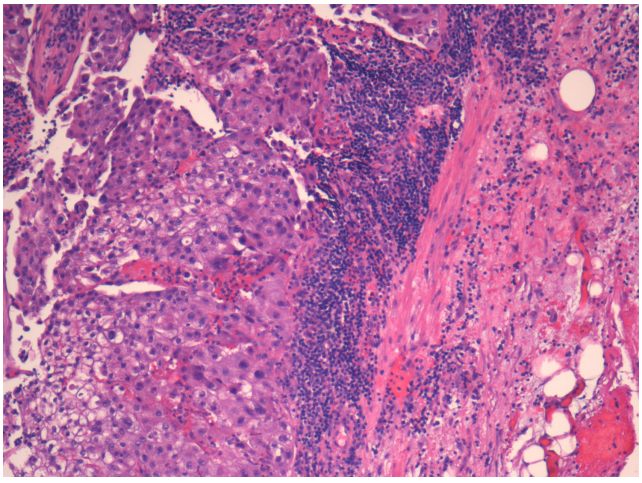

FIGURE 5 Spine lymph node metastasis from poorly differentiated adenocarcinoma (b. 16678.17 HEx10) [Colour figure can be viewed at wileyonlinelibrary.com]

preferred sites, while concerning soft tissue, the gingiva is the most commonly affected.[18]

Maxillofacial metastases have been reported to be more prevalent among males than females (ratio 1.3:1),[18] among those, the posterior mandible is the most common location for metastases both in male and female gender, although in the condylar region, males are more affected than females (ratio 2:1).[19]

Metastases have a predilection for the marrow of haematopoietically active bone tissue, inasmuch red marrow is richer in sinusoids that facilitate neoplastic clones to colonise and proliferate.[23]

Jaws' metastatic disease is mainly situated in the red marrow which is predominant in the posterior mandible, ascending ramus and angle, where hematopoietically active bone marrow is present instead of the maxilla which has predominantly fatty marrow.[18,24,25] These sites attract tumour cells, thus explaining their greater tendency to metastasize compared to other cancers.[19,24,25]

Even though the mandible is not an important haematopoietic site, especially in older patients, remnants of haematopoietic marrow can be found in the posterior portions of the mandible, mainly in cases of focal osteoporotic bone marrow defects.[19,23]

In addition, a conceivable mechanism to explain the mandibular localization of metastases consists of a process mediated by bone morphogenetic proteins (BMPs), endothelin-1, Wnt family ligands, and platelet-derived growth factor (PDGF) which are osteoblast stimulating factors, promoting osteoblastic metastasis.[18] For example, in metastatic prostate carcinoma, homeostasis of RANK and RANK-L is disturbed by osteoprotegerin secretion; osteoprotegerin is a RANK-L inhibitor and decreases osteoclastic activity and this could explain the presence of osteo-thickening metastases.[18]

On the other hand, factors such as insulin-like growth factor (IGF) and transforming growth factor-β (TGF-β) produced by tumour cells, elicit osteoclast activating factors like RANK-L which can lead to osteo-rarifying metastases.[18]

These different mechanisms can explain the production of osteo-rarifying or osteo-thickening metastases.

Possible routes of metastasis include the bloodstream and lymphatic system, although the majority of metastases occur hematogenously.[19,26] Specifically, Kanth et al. suggested that the main mechanism of hematogenous metastasis to the oral cavity involves Batson's venous plexus, the valveless prevertebral venous network that permits the retrograde path of tumour cells from the lungs to the face.[19,27] Metastatic lesions can be found anywhere in the oral cavity, yet 90% of them have an intraosseous localization, while soft tissue localizations are rare.[28] Labrador et al. in a more recent review estimate that osseous invasion corresponded to 65%–75% of the cases, while soft tissue invasion corresponded to 25%–35%. It is quite impossible to determine whether these are primarily soft tissue or bone tissue lesions because it is often a combination of soft and bone tissue involvement.[18] In soft tissue, the gum was the most affected site[18,19]; according to Labrador et al., the presence of chronically inflamed gingiva and rich capillary networks may attract metastatic tumour cells.[18]

In a chronically inflamed gingiva capillary vessels constantly proliferate and may result in fragmentation of basement membranes of immature capillaries[19] with an increase of their permeability.

Clinically, metastases localised in oral soft tissues can mimic reactive overgrowth or other malignancies such as squamous cell carcinoma, mesenchymal tumours, lymphomas or primary bone malignancies.[18]

Generally, the presence of oral and maxillofacial metastasis is suspected after OPG or intraoral x-rays execution; when the clinician the suspect of malignancy a second-level radiological exam is required and it can permit to precisely evaluate the localization and morphology of the lesion.

It should be remembered that ill-defined radiolucency could be features of malignancy but are not specific, therefore several investigations must be performed.

Labrador et al found that in over 94% of cases, bone metastases were osteolytic, while only 4% were osteodensifying (for example metastasis from prostate cancer); these findings are similar to the ones reported by Hirshberg et al.[18,20]

Radiographically osteolytic lesions appear as radiolucent areas with thinned or absent trabeculae and ill-defined margins, sometimes with a worm-eaten appearance that can resemble osteomyelitis, as in the present case. On the contrary, sclerotic metastases appear as nodular, rounded and fairly well circumscribed because of the thickened coarse trabeculae.[29]

Clinical manifestations of jawbone metastasis can be highly variable, with most patients presenting pain, toothache, swelling, paresthesia, bleeding, superinfection, dysphagia, interference with mastication and disfigurement. Furthermore, mandibular metastases may simulate temporomandibular disorders, osteomyelitis, trigeminal neuralgia[26] or even trismus, which is often associated with condylar lesions.[19] In the case of our patient, the involvement of the mandibular bone was so extensive that it caused the condyle fracture, highlighting the related symptoms. Before this event, no symptoms were present.

Special attention should be given to patients who develop "numb chin syndrome" or mental nerve neuropathy, that is hypoesthesia or paresthesia in an area over the chin and lower lip, within the distribution of the mental or inferior alveolar nerves. The presence of this symptom should always be alarming for potential metastatic disease.[20]

In metastatic disease, endothelin-1 (ET-1) is thought to be involved in both pain and tumour outgrowth; ET-1 has two different receptors which are endothelin A (ETAR) and endothelin B (ETBR) and it seems that ETAR activation is involved in bone metastases pain.[30,31]

Tumour cells and associated inflammatory (immune) cells stimulate several chemical mediators, including prostaglandins (PGE2), nerve growth factor (NGF), endothelins (ET-1) and bradykinin (BK), which can directly activate or sensitise nociceptors, promoting pain.[18]

Diagnosis of metastatic tumour is possible if primary cancer is clinically and histologically verified. In fact, metastasis must be the same histological subtype as primary cancer; if the primary lesion is unknown immunohistochemistry can be valuable to hypothesize the origin of a metastatic lesion. Moreover, molecular characterisation is increasingly used to further analyse both primary and metastatic lesions.[18]

TMJ tumours, both benign and malignant, are rare and difficult to diagnose,[32] in fact, at the onset, they resemble common TMJ disorders and can lead the specialist astray from formulating the correct diagnostic suspicion. In the case of non-specific maxillo-mandibular symptoms it is mandatory to perform an OPG, moreover, in patients unresponsive to treatment for TMJ, in the differential diagnosis process, metastatic disease should be included. A CT scan or Magnetic Resonance Imaging (MRI) in the case of TMJ involvement should be part of the diagnostic procedure.[33]

Metastasis to the oral and maxillofacial region is reported to account for 1% to 1.5% of all oral and maxillofacial malignancies. Metastases have been the first clinical evidence of cancer in almost 20%–31% of the cases, emphasising that a significant number of primary tumours are unknown at the time of the oral presentation.[18,19,25] Labrador et al. showed that only 37.5% of patients had had a previous cancer diagnosis at the time of metastasis diagnosis.[18]

Generally, the presence of oral metastasis is a manifestation of advanced-stage disease, which is often related to multiple metastases in other locations, that leads to a poor prognosis, up to 90% of mortality.[18]

Labradors et al. have summarised the case reports of the last 40 years and they showed an average survival after the diagnosis of oral metastasis of 9.8 months for both genders, 10.5 months for females, and 9.2 months for males,[18] which is slightly different from Hirshberg et al. and Kirschnick et al, who found an average survival of 7 and 8 months respectively.[19,20] Kirschnick et al. also report that 3-year and 5-year survival rates are 17.7% and 7.3%, respectively.[19]

Biopsy is essential to reach the correct diagnosis although in metastatic disease the prognosis is poor since metastases are generally features of advanced disease and are treated with palliation or limited surgery to improve the patient's quality of life.[18,19]

4 | CONCLUSION

It is important to remember that in patients with an established diagnosis of lung cancer any radio-transparent lesion of the jaw or an unexplained painful symptomatology to the oro-maxillo-facial complex, should be placed in differential diagnosis with metastasis of the primary tumour.

The diagnosis is fundamental, however, the timing of the maxillofacial diagnosis does not seem to influence the prognosis, because the maxillofacial metastases are rare and their manifestation indicates advanced disease with a poor chance of survival after 5 years.

AUTHOR CONTRIBUTIONS

Erica Vettori: collected data, wrote and revised the manuscript; Alberto Borella: wrote the manuscript; Fulvia Costantinides: revised the manuscript; Roberto Rizzo: contributed to literature revision; Michele Maglione: has treated the patient, contributed to data collection and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Azienda Sanitaria Universitaria Giuliano Isontina (ASU GI). Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the author(s) with the permission of Azienda Sanitaria Universitaria Giuliano Isontina (ASU GI).

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