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Case report

The mandibular condyle as uncommon metastatic site of neuroendocrine carcinoma: Case report and review of literature

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ABSTRACT

Temporo-mandibular joint (TMJ) metastases are a very rare event and only 73 cases are reported in literature. In about 40% of cases condylar metastases represent the first clinical manifestation of a tumor of elsewhere and may then allow an early diagnosis. However, the identification of this tumoral process can be difficult as in over 50% of the cases it has a nuanced clinical presentation that is very similar to temporo-mandibular disorders.

The first case of metastatic neuroendocrine carcinoma (NEC) of the temporo-mandibular joint (TMJ) mimicking a temporo-mandibular joint disorder is presented in this report. Furthermore, an extensive review of the literature has been performed in order to establish a correct diagnostic–therapeutic protocol for these oncologic patients.

1. Introduction

Primary neoplasm of the mandible are more common than metastatic disease, which represents only 1% of such tumors [1]. Metastases are more commonly seen in the hematopoietically active marrow of the skeletal bones. The cancellous bone at these levels is indeed rich with sinusoidal vascular spaces that permit tumor cells penetration. The mandible is not a site of active marrow in humans, particularly in older individuals. When cancellous marrow is present, it is usually in the posterior aspect of the mandible [2].

If metastatic tumors of the mandible are rare, involvement of the mandibular condyles by such growths is even rarer and, since the first description by De Cholnoky in 1941 [3], only 73 cases are reported in international literature.

An unusual case of metastatic neuroendocrine carcinoma (NEC) of the temporo-mandibular joint (TMJ) is described in this report. The caecum was the site of arising of the primary tumor. This is the first report of metastatic TMJ involvement of a NEC.

2. Case report

A 66-year-old Caucasian man presented with an episode of acute intestinal obstruction. His medical history included chronic ischemic heart disease, hypercholesterolemia and hypertension. He was therefore hospitalized at the Department of Surgery.

A total body CT scan was then executed showing a 9 cm caecal mass with infiltration of the last ileal loop and the appendix. A regional lymphonodal involvement and the presence of a single liver metastasis were revealed. The patient underwent immediate right colectomy with contemporary resection of the hepatic metastasis. Histological examination revealed a Large Cell NEC of the large bowel. The intestinal mucosa was infiltrated by a proliferation of tumor cell faintly arranged in a organoid growth pattern. The tumor was composed of large cells layers with scant cytoplasm and enlarged, pleomorphic nuclei. Numerous apoptotic bodies and mitotic figures were observed. High power magnification of the tumor showed glandular differentiation and prominent intracytoplasmic mucin vacuoles, yielding a "signet ring cell" appearance. Tumor cells showed immunoreactivity for chromogranin and Ki-67; labeling index was 95% (Fig. 1).

☆ AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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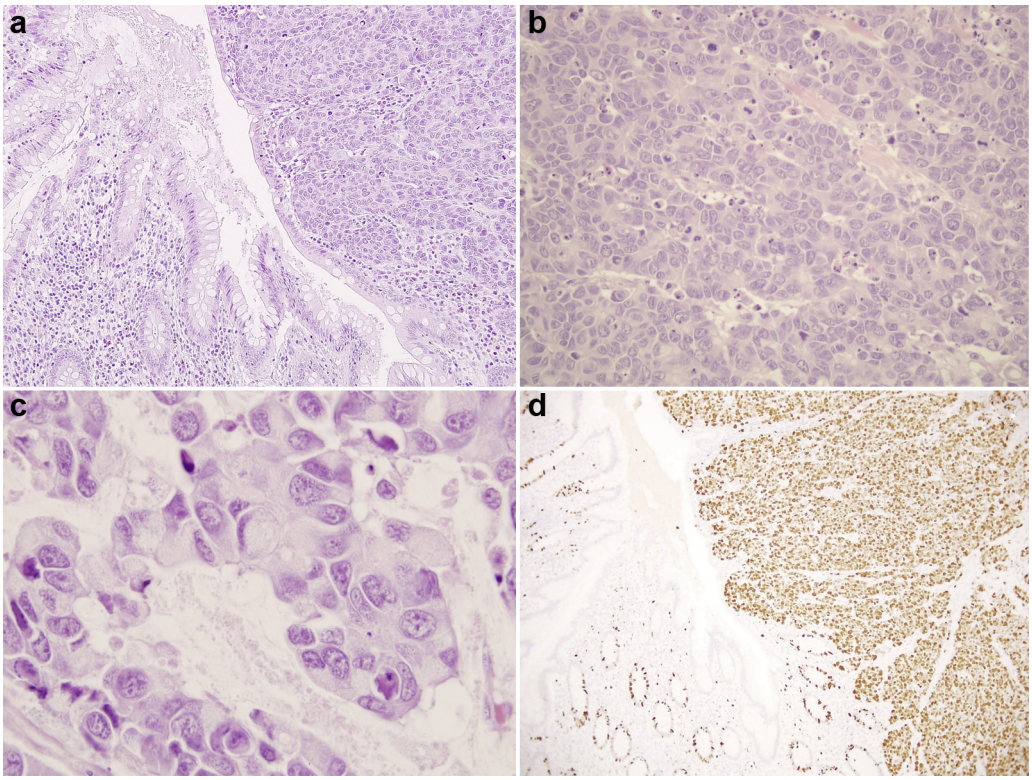

Fig. 1. Histologic features of caecum NEC. A (H&E, 20×): The intestinal mucosa is infiltrated by a proliferation of tumor cell faintly arranged in a organoid pattern. B (H&E, 40×): The tumor is composed of sheets of large cells with scant cytoplasm and enlarged, pleomorphic nuclei. Numerous apoptotic bodies and mitotic figures are observed. C (H&E, 100×): High-power magnification of the tumor showing glandular differentiation and prominent intracytoplasmic mucin vacuoles of tumors cells, yielding a "signet ring cell" appearance. D (Peroxidase stain, 40×): The tumor cells show immunoreactivity for chromogranin. Ki-67 labeling index was 95%.

During the post-operative period the patient complained ingravescent right TMJ pain and was referred to Maxillo-Facial Surgery Department for evaluation.

He reported that, actually, right TMJ pain and limitation of jaw movements started about 8 months before. For that problem he already turned to his dentist that, in the suspicion of a TMJ disorder, prescribed NSAIDs and myorelaxant therapy. Two weeks after, due to the symptoms persistence, the patient performed radiological exams. Orthopantomograph and dynamic TMJ radiographs were totally negative. TMJ magnetic resonance, of which the patient had no images, referred anterior displacement of the right disk, without reduction, intra-articular effusion and morphological alterations of the condyle compatible with arthritic degeneration. Clinical and radiological diagnosis of not reducible TMJ disk anterior displacement was then made and the patient begins a conservative therapy with occlusal bite that was continued, without any benefit, for 5 months until the admission at the Department of Surgery.

Clinical examination of the patient did not show masses or swelling of the right TMJ, masticatory muscles appeared contracted and painful. The patient complained pain both at rest (VAS 5) and during mandibular movement (VAS 9). Maximum mouth opening was 15 mm with right deviation; left lateral excursion was 2 mm whereas there was no restriction of the right lateral excursion. Parotid glands secretion was clear and the patient did not show cervical lymphadenopathy. The oral cavity inspection was normal. There was deep bite, Class II occlusion with complete molar edentulism.

To investigate the presence of a TMJ metastatic lesion, maxillofacial contrasted CT scan was then performed showing structural subversion of the right condyle with osteosclerotic areas alternate to 3–5 mm in diameter osteolytic lesions. The periosteum and

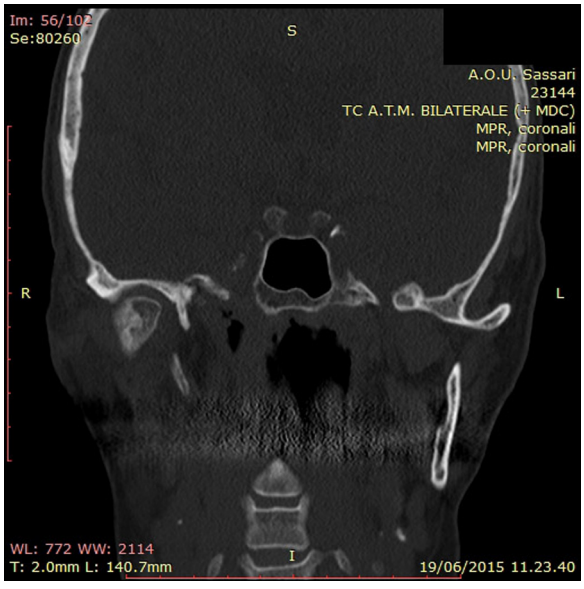

Fig. 2. Right TMJ CT-scan showing osteosclerotic areas alternate to 3–5 mm in diameter osteolytic lesions.

the lateral pterygoid muscle presented increased thickness and oedema without others significant alterations (Fig. 2).

The patient was submitted to open biopsy, frozen sections confirmed the malignancy suspicion. Condylectomy with healthy margins was then performed in the same surgery (Fig. 3). Definitive histologic examination confirmed the diagnosis of metastatic lesion showing epithelial scattered signet-ring cells containing intracytoplasmic mucina and poorly formed glandular lumen arranged in

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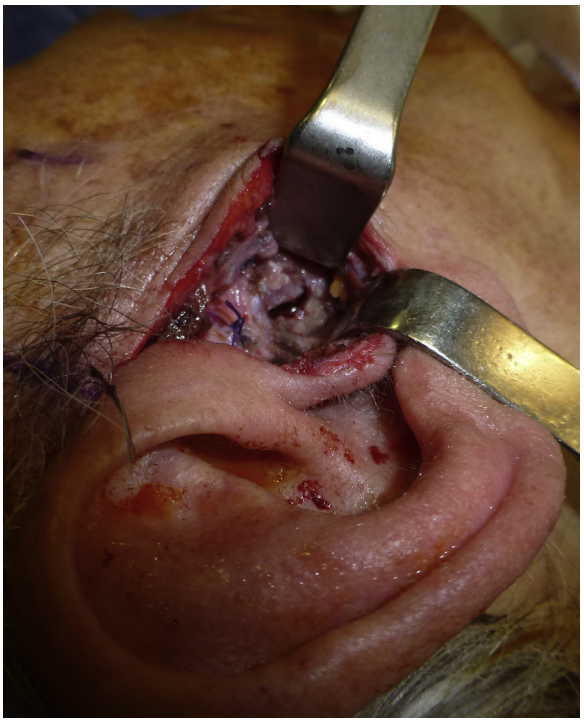

Fig. 3. Intraoperative view showing the right temporo-mandibular joint.

clusters and island growing within the bone. Tumoral cells were immunoreactive for chromogranin A and Ki-67, labeling index was 80% (Fig. 4).

After surgery, the patient was subjected to regional radiotherapy associated with chemotherapy (streptozotocin in combination with 5-fluorouracil). Three months after surgery a new total body CT scan has been executed showing the appearance of pulmonary and hepatic metastases. The rapid deterioration in the patient's condition led to his death six months after diagnosis.

3. Discussion

NEC of the colon and rectum are quite rare, representing approximately 0.3–0.1% of all colorectal carcinomas [4,5]. The growth patterns and cytological features are typical of neuroendocrine tumors. The presence of neurosecretory granules in the cytoplasm of tumor cells detected by electron microscopy is characteristic. Furthermore, neuroendocrine carcinomas typically stain for the immunohistochemical markers synaptophysin, chromogranin, or neuron-specific enolase. Compared with colo-rectal adenocarcinomas, NEC have a significantly poorer prognosis and most patients (around 70%) had metastatic disease at the time of diagnosis. The metastatic pattern is relatively consistent and includes regional lymphatics and lymphnodes, other than the liver and the lungs [6]. Bone metastases are less common, although their frequency is increasing due to improvements in surgical and medical management of these patients.

Bone metastases mechanism of NEC showed the spread of neoplastic cells from the primary tumor invading blood vessels and spreading as emboli to distant regions, such as the bone. Malignant tumor cells adhere to blood vessel to enter the bone matrix through extravasations, were they then proliferate. NEC's cells produce different chemokines, thus both osteoblastic and osteolytic metastases can be observed [7].

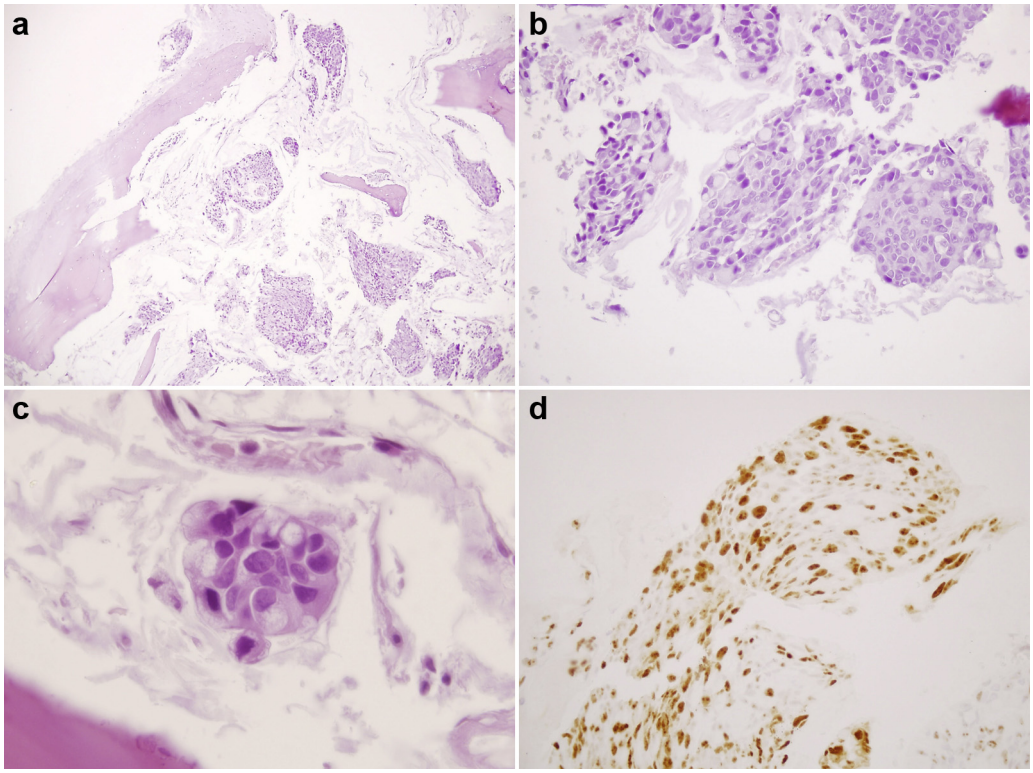

Fig. 4. Histologic features of condylar NEC metastasis. A (H&E, 4×): Epithelial tumor cells arranged in clusters and islands are growing within the bone. B (H&E, 40×): Clusters of carcinoma cells show scattered signet-ring cells containing intracytoplasmic mucina and poorly formed glandular lumen. C (H&E, 100×): Small cluster of epithelial carcinoma cells show a signet-ring appearance with cell containing intracytoplasmic mucina. D (Peroxidase stain, 40×): The tumor cells are immunoreactive for chromogranin A and Ki-67. The labeling index is 80%.

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Table 1
Report of condylar metastasis in international literature (1941–2016) [Abbreviations: NR: not reported; w: week; m: month; y: year].

Authors	Previous malignancy	Presenting symptoms	Primary site	Tumor type	Treatment	Prognosis
De Cholnoky, 1941 [3]	Yes	Not reported	Toe	Melanoma	NR	NR
Thoma, 1947 [11]	No	TMJ dysfunction	Unknown	Adenocarcinoma	NR	NR
Thoma, 1947 [11]	No	TMJ dysfunction	Unknown	Transitional cell carcinoma	NR	NR
Salman, 1954 [12]	1 m before	Hard mass	Uterus	Squamous cell carcinoma	None	Died 3 m later
Blackwood, 1956 [13]	3 m before	Swelling and trismus	Breast	Adenocarcinoma	None	Died 4 m later
Ameli, 1965 [14]	No	Not reported	Lung	Bronchogenic carcinoma	NR	NR
Worth, 1966 [15]	No	TMJ dysfunction	Rectum	Adenocarcinoma	NR	NR
Epker, 1969 [16]	5 y before	Pathologic fracture	Breast	Adenocarcinoma	RT	Died 1 m later
Hartman, 1973 [17]	5 m before	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Agerberg, 1974 [18]	2 y before	TMJ dysfunction	Breast	Adenocarcinoma	RT/CT	Died 5 m later
Butler, 1975 [19]	2 y before	TMJ dysfunction	Breast	Melanoma	NR	NR
Mace, 1978 [20]	3 y before	Swelling, trismus and mental paresthesia	Breast	Adenocarcinoma	Tumor resection	Died 6 m later
Wolujewicz, 1980 [21]	No	Swelling	Prostate	Adenocarcinoma	RT	Died shortly after
Mizukawa, 1980 [22]	3 y before	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Compère, 1981 [23]	No	Swelling and trismus	Lung	Bronchogenic carcinoma	NR	NR
Compère, 1981 [23]	No	Swelling and trismus	Pancreas	NR	NR	NR
Compère, 1981 [23]	6 m before	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Donazzan, 1981 [24]	21 y before	TMJ dysfunction	Lung	Bronchogenic carcinoma	NR	NR
Gerlach, 1982 [25]	NR	Swelling and pain	Lung	Bronchogenic carcinoma	RT	Died 8 m later
Giles, 1982 [26]	6 y before	TMJ dysfunction	Rectum	Adenocarcinoma	NR	NR
Peacock, 1982 [27]	No	TMJ dysfunction	Lung	Bronchogenic carcinoma	RT	Died 3 m later
DeBoom, 1985 [28]	No	Pathologic fracture	Prostate	Adenocarcinoma	NR	NR
Owen, 1985 [29]	No	TMJ dysfunction	Lung	Adenocarcinoma	NR	NR
Hecker, 1985 [30]	No	TMJ dysfunction	Unknown	Adenocarcinoma	NR	NR
Tatcher, 1986 [31]	NR	Swelling	Prostate	Adenocarcinoma	NR	NR
Sokolov, 1986 [32]	12 y before	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Sokolov, 1986 [32]	6 y before	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Lowicke, 1987 [33]	Yes	Not reported	Kidney	NR	NR	NR
Gormann, 1987 [34]	No	TMJ dysfunction	Prostate	Adenocarcinoma	NR	NR
Webster, 1988 [35]	2 y before	Not reported	Lung	Bronchogenic carcinoma	NR	NR
Webster, 1988 [35]	Yes	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Cuttino, 1988 [36]	2 y before	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Rubin, 1989 [37]	No	TMJ dysfunction	Unknown	Adenocarcinoma	NR	NR
Catrambone, 1990 [38]	Yes	Swelling	Prostate	Adenocarcinoma	NR	NR
Karr, 1991 [39]	21 m before	TMJ dysfunction	Left foot	Synovial sarcoma	NR	NR
Lalaikos, 1992 [40]	Yes	Swelling	Liver	Hepatocellular carcinoma	NR	NR
Van Rensburg, 1992 [41]	2 y before	TMJ dysfunction	Unknown	Adenocarcinoma	NR	NR
MacAfee, 1993 [42]	NR	Swelling, paresthesia of the lip	Colon	Adenocarcinoma	NR	NR
Stavropoulos, 1993 [43]	7 y before	TMJ dysfunction	Breast	Adenocarcinoma	NR	NR
Johal, 1994 [9]	No	TMJ dysfunction	Kidney	Clear cell carcinoma	CT	Died 18 m later
Nortjé, 1996 [44]	2 y before	TMJ dysfunction	Nose	Melanoma	CT	Died 6 m later
Porter [45]	Yes	Swelling and pain	Testicle	Teratoma	RT	Died 5 m later
Beck-Managetta, 1997 [46]	1 y before	Swelling	Lung	Adenocarcinoma	RT	Alive after 18 m
Cohen, 1998 [47]	No	TMJ dysfunction	Unknown	Squamous cell carcinoma	NR	NR
Kolk, 2003 [48]	Yes	TMJ dysfunction	Stomach	Adenocarcinoma	Tumor resection + RT/CT	NR
Deeming, 2003 [49]	3 y before	TMJ dysfunction	Breast	Cystosarcoma Phyllodes	RT	Died 6 m later
Smolka, 2004 [50]	2 y before	Swelling, pain and malocclusion	Stomach	Adenocarcinoma	Tumor resection + RT	Alive after 8 m
Mason, 2005 [1]	No	Hard mass	Rectosigmoid colon	Adenocarcinoma	None	Died shortly after
Kaufmann, 2005 [51]	Yes	TMJ dysfunction	Lung	Bronchogenic carcinoma	RT	NR
Duker, 2006 [52]	Yes	TMJ dysfunction	Breast	NR	NR	NR
Miles, 2006 [53]	19 y before	TMJ dysfunction	Breast	Adenocarcinoma	Tumor resection	NR
Menezes, 2008 [54]	No	Swelling and pain	Breast	Adenocarcinoma	NR	NR
Kamatani, 2008 [55]	3 y before	Swelling and pain	Liver	Hepatocellular carcinoma	RT/CT	Alive 1 y later

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Table 1 (*Continued*)

Authors	Previous malignancy	Presenting symptoms	Primary site	Tumor type	Treatment	Prognosis
Boniello, 2008 [56]	No	TMJ dysfunction	Lung	Adenocarcinoma	Tumor resection	Died 6 m later
Schulze, 2008 [57]	No	TMJ dysfunction	Lung	Bronchogenic carcinoma	Biphosphonates	NR
Gomes, 2009 [58]	No	Hard mass	Unknown	Adenocarcinoma	NR	Died 4 m later
Kruse, 2010 [59]	No	Hard mass and pain	Lung	Bronchogenic carcinoma	CT	Died 4 w later
Kruse, 2010 [59]	9 y before	Pathologic fracture	Tyroid	NR	NR	NR
Kruse, 2010 [59]	No	Swelling, pain and trismus	Lung	Adenocarcinoma	None	Died 2 w later
Katsnelson, 2010 [60]	No	Swelling, pain and trismus	Lung	Bronchogenic carcinoma	RT/CT	NR
Cristofaro, 2011 [61]	No	Swelling and pain	Prostate	Adenocarcinoma	Tumor resection + RT/CT	Alive after 2 y
Cristofaro, 2011 [61]	NR	Swelling and trismus	Kidney	Clear cell carcinoma	Tumor resection + CT	Alive after 8 m
Patricia, 2011 [62]	Yes	TMJ dysfunction	Breast	Adenocarcinoma	RT	Died 6 m later
Kelles, 2021 [63]	3 y before	Swelling and trisums	Kidney	Clear cell carcinoma	RT/CT	NR
Scolozzi, 2012 [64]	No	TMJ dysfunction	Lung	Large cell carcinoma	RT/Ct	Died 6 m later
Freudlsperger, 2102 [65]	5 y before	TMJ dysfunction	Prostate	Adenocarcinoma	RT/CT	NR
Puranik, 2013 [10]	Yes	Asymptomatic	Uterine cervix	Squamous cell carcinoma	RT/CT	NR
Qiu, 2013 [8]	No	Swelling	Prostate	Adenocarcinoma	Tumor resection + CT	Died 1 y later
Qiu, 2013 [8]	6 m before	Swelling and numbness	Penis	Squamous cell carcinoma	Chemotherapy	Died 3 m later
Qiu, 2013 [8]	No	Swelling and pain	Bladder	Adenocarcinoma	Tumor resection + CT	Died 6 m later
Qiu, 2013 [8]	6 y before	Swelling and pain	Colon	Adenocarcinoma	Chemotherapy	Died 3 m later
Qiu, 2013 [8]	No	TMJ dysfunction	Lung	Bronchogenic carcinoma	Chemotherapy	Died 6 m later
Qiu, 2013 [8]	4 y before	TMJ dysfunction	Breast	Adenocarcinoma	Tumor resection + CT	Alive after 1 y

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Best to our knowledge, this is the first report of NEC metastatic spread to TMJ. The frequency of metastatic spread of any malignancy to the mandibular condyle is low for unknown reasons. It may possibly reflect the poor local blood supply, the lack of hemopoietic marrow, the presence of bone cortex that limits the spread of synovial malignancy into the marrow of the condyle or the fact that hematogenous metastases to such a minor joint usually represents the final stage of malignant disease, where generalized metastases already should be clinically present [8–10].

Since 1941 only 73 cases of TMJ metastases have been reported. Table 1 shows the framework summary of the results of our extensive review.

Patient's ages ranged from 15 to 85 (mean 57,7 years), 32 patients were male and 38 female, in 3 cases genre was not reported. Adenocarcinoma is the most common histotype founded in TMJ metastases (56,1%), followed by squamous cellular carcinoma (20,5%), melanoma (4,1%), clear cell carcinoma (4,1%), hepatocellular carcinoma (2,7%), synovial cell sarcoma (1,3%), large cell carcinoma (1,3%), transitional cell carcinoma (1,3%), teratoma (1,3%) and cystosarcoma phyllodes (1,3%). Regarding the metastases origins the most common primary tumor sites were breast (27,6%), lung (21%), prostate (10,5%), large bowel and rectum (6,5%), kidney (5,2%), uterus (3,9%), liver (2,6%), foot (2,6%), bladder (1,3%), pancreas (1,3%), tyroid (1,3%), testicle (1,3%) and penis (1,3%). In 9,2% of the cases primary tumor remained unknown. It's important to emphasize that TMJ metastasis, sign of advanced metastatic disease, was the first tumoral manifestation in 28 patients (36,8%).

The lack of any other oncologic sign or symptom made the diagnosis very difficult in these cases. When history of malignancy was present, TMJ metastasis appeared with a variable latency between 1 month to 21 years after the first cancer diagnosis. Even clinical presentation is highly variable and often nonspecific. Preauricolar swelling, masses or pathological fractures are present in 42.4% of the patients only. In 50,6% of the cases clinical presentation is nonspecific and, as in our case, broadly comparable to a mandibular dysfunction: limitation or alteration of mandibular movements, pain, clicks and crepitations without any sign of tumor. This nuanced clinical presentation can thereby significantly delay the correct diagnosis. The symptoms can be mistaken as caused by mandibular disorders, osteomyelitis or dental problems. The non specificity of the clinical presentation is reflected in a radiological picture highly variable: are represented aggressive TMJ destructive masses and less defined osteolytic or osteoblastic alterations. For this reason conventional radiographs are not particularly sensitive in identifying metastatic lesions [45]. Radioisotopic scannings (Scintigraphy, SPECT, PET/CT) can show an abnormal uptake of bone-seeking isotopes before that a lesion can be identified on plain radiographs, but are not specific and may not detect metastatic tumors with minimal or absent osteoblastic activity. PET/CT detects the abnormal glycometabolism of malignant tumor cells that is quite different from normal cells and benign tumor cells. However it has some limitation in distinguishing inflammation from malignancy [8].

Open biopsy or fine-needle biopsy are therefore necessary for the correct diagnosis.

The prognosis of mandibular metastases is very poor. Patient survival ranged from 2 weeks to 18 months, with a medium life expectancy of approximately 3 months. For patients with condylar metastases, the low survival rate may be explained because there are often multiple concurrent metastases in the late stage of disease [8]. For patients with multiple metastases, the most common treatment approach was combined palliative radiotherapy and chemotherapy.

Surgical TMJ metastatic resection and adjuvant radiotherapy seem to be indicated only when it is a solitary metastases and the primary disease is controlled [8,50,53,61].

4. Conclusions

In all the TMJ diseases, primary or metastatic condylar tumors should be included in the differential diagnosis, especially when the symptoms do not respond to treatment and in patient with an history of malignancy.

In these cases, contrasted CT scan or MRI should be always part of the diagnostic procedure.

However, these lesions are often a sign of advanced neoplastic disease with very poor prognosis leaving place for surgery only in a few selected cases.

Ethical approval

This study is approved by University of Sassari Ethical committee.

Conflict of interest

The authors declare that they have no conflict of interest.

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