CLINCAL CASE

MALIGNIZED BRANCHIAL CYST OR CERVICAL METASTATIC ADENOPATHY WITH PRIMARY TUMOR IN A TONSILLAR HIDDEN CARCINOMA?

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Abstract

Cancer of occult origin is defined as a group of primary tumors with metastatic determinations, most commonly lymph nodes for which diagnostic algorithms fail to identify the place of origin of the primary tumor at the time of positive metastasis diagnosis. Squamous cell carcinoma with a truly unknown primary office is a relatively rare entity in the region of the head and neck. Retrospective studies suggest that it accounts for 1-3% of new cases of squamous cell carcinoma of the head and neck. We will present the clinical case of a 76-year-old patient with metastatic left-cervical cystic adenopathy, initially interpreted as a malignant branchial cyst. Discrepancies in histopathological examination, imaging and clinical examination delayed the performance of adjuvant radiotherapy. We will present details of diagnosis and evolution of the case. The results of the systematic literature review suggest that palatal tonsillectomy has a high overall rate of detection of subclinical primary tumors. Given the significant number of bilateral / contralateral occult tonsil tumors reported in the specialty literature, bilateral tonsillectomy should be considered in determining the diagnosis of squamous cell carcinoma patients of unknown primary origin in the head and neck. Cervical lymph node metastasis with unknown primary tumor remains a difficult topic for head and neck oncology. Most diagnostic and treatment protocols recommend unilateral or bilateral tonsillectomy, with an increased chance of finding an occult tumor in the palatine, unilateral or bilateral tonsils. In the presence of a cystic cervical lymph node metastasis, the first location should be considered as the primary tumor site must be the palatine tonsil.

Keywords*: primitive metastatic adenopathy, tonsil, surgery, adjuvant radiotherapy*

Introduction

Occult cancer is defined as a group of primary tumors with metastatic determinations, most commonly in lymph nodes for which diagnostic algorithms fail to identify the place of origin of the primary tumor at the time of positive metastasis diagnosis. Recent literature data show that primary carcinoma-like tumors with metastasis in cervical lymph nodes account for approximately 2-9% of all malignancies of the head and neck [1]. For squamous cell carcinoma metastases, it is appreciated that the occult site of the tumor may be the head and neck, lung, cervix, penis, vulva, bladder [2]. Squamous cell carcinoma with a truly unknown primary office is a relatively rare entity in the region of the head and neck. Retrospective studies suggest that it

accounts for 1-3% of new cases of squamous cell carcinoma of the head and neck [3]. Guidelines have been published for the diagnosis and treatment of cancer of occult origin, in order to facilitate the identification of a primary tumor in patients with metastatic cervical adenopathy [1,2,4].

Regarding the evolution in patients with metastases of squamous cell carcinoma of the head and neck, with primitive tumor of occult origin have clinical and prognostic characteristics similar to those patients with cervical lymph node metastases of carcinoma where the primary tumor site is known. Regarding multimodal treatment, locoregional cancer control improved in this category of patients, but there were only a few improvements in survival rate after treatment. The survival rate after treatment at 3 years is 40-60% and at 5 years 10-25%. In conclusion, the prognosis is reserved despite therapeutic advances [5].

The most common sites for occult carcinomas with cervical lymph node metastases of squamous cell carcinoma are the palatine tonsil, tongue base, rhino pharynx, piriform sinus. Cystic metastasis is encountered in cases with primary tumor at the level of palatine tonsils and thyroid carcinomas. It may be mistaken for branchial cysts [5].

Case presentation

We present the case of a 76-year-old patient who was sent by a family doctor in July 2013 for a specialist consultation for the diagnosis of Sjogren's Syndrome and left subangulomandibular adenopathy with recent onset (2 weeks). Laboratory tests, abdominal ultrasound, pulmonary X- ray were performed and they were between normal limits. ENT clinical examination and nasal endoscopy - no tumor formations were visualized. Cervical MRI examination reveals left cervical necrosis nodular mass, most likely adenopathy; other small left internal jugular satellite adenopathy without necrosis; inflammatory-edematous changes in the left palatine tonsil; it is appreciated that the left cervical adenopathy does not clearly belong to the clinical picture of Sjogren's disease and that, rather, it appears to be a secondary determination of a primitive tumor in the area of ENT, thyroid or lung and the excision of the lymph node with histopathological and immunohistochemical examination is indicated in a clinic of OMF surgery.

Under general anesthesia, it is practiced to remove the left cervical adenopathy. Two lymph ganglions were removed, “one with a diameter of 0.5 cm, which proved to be reactive and the other with a diameter of 3 cm, round, in translucent section, with whitish and yellowish areas, matte, having a creamy consistency, apparently separated in lobes, which turned out to be a cystic adenopathy metastasis of squamous cell carcinoma, without exceeding the lymph ganglionic capsule”, according to the first histopathological result. A second opinion was also practiced for the histopathological result that revealed “malignancy cyst - epidermoid carcinoma (keratinizing squamous), with pericystic lymphocyte infiltrate”. The histopathologist's conclusion was “that it is difficult to specify whether the tumor is primary (malignant pleomorphic adenoma or vestigial malignant branchial cyst) or secondary (carcinomatous metastasis); additional IHC tests are recommended to determine the primary or secondary origin and we considered for the primary origin of tumor proliferation”.

Repeat analysis of blocks and slides, this time supplemented with IHC tests (CK 34betaE12-positive diffuse, EGFR-negative, Ki67-positive diffused, P16-positive diffused, EBV-negative). For the small lymph node sinus histiocytosis is reconfirmed, and for the large lymph node, “moderate differentiated keratinizing squamous cell carcinoma (G2) apparently developed in a cystic structure probably belonging to a branchial cyst” (Figure 1). Commentary on the analysis shows that “IHC tests cannot completely exclude a cystic metastasis of squamous cell carcinoma; squamous cell carcinomas with minimal keratinization, metastatic, lateral cervical with unknown starting point, diffuse positive for P16 are more than 90% associated with HPV and origin in the palatal or lingual tonsils; HPV testing is indicated by IHC/ PCR/ Hybridization”. As a result of this last recommendation, a gynecological check is performed and the Pap smear analysis in a liquid medium whose conclusion is “Negative for an

intraepithelial or malignant lesion". HPV genotyping detection test by PCR method showed that "The presence of DNA-HPV for the main HPV strains of high, medium and low oncological risk was not highlighted".

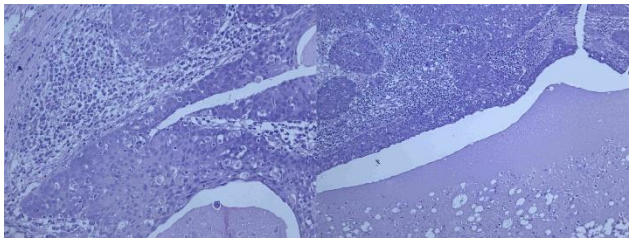

Figure 1 – Keratinizing squamous cell carcinoma developed in a cystic structure

The investigations continued with native thoracic-abdominal-pelvic CT and IV contrast that did not find "thoracic-abdominal-pelvic tumor masses". Then with native cervical MRI and IV contrast that described "Changes in the level of the left palatine tonsil, with a stationary aspect compared to the August 2013 MRI examination, to be correlated with the ENT examination and small bilateral cervical ganglionic images without necrosis" (Figure 2). A second opinion on this MRI observes "Slight asymmetry of palatine tonsils, without certain tumor aspect; latero-cervical and submandibular lymph nodes, most likely of inflammatory etiology". There was also a general dermatological consultation and no tumor signs were found. The biological samples were within normal limits, with ESR value of 25 mm/1 h. Also, tumoral markers SCC (0.7 mg/dl) had insignificant values.

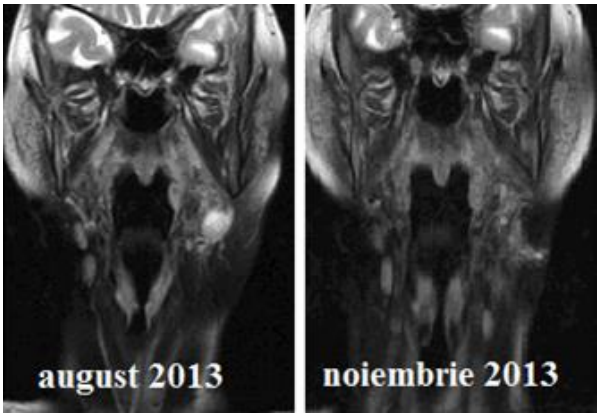

Figure 2 – Cervical IRM in evolution – hypersignal at the level of the left palatine tonsil without certain tumor character (before and after the ablation of the left lateral cervical cystic metastatic adenopathy)

Due to the fact that the tumor remained hidden, PET / CT was recommended and approved with the diagnosis "left submandibular lymph node metastasis with unspecified starting point, operated "and for the purpose of" evaluation possible departure point for establishing therapeutic indication ". The PET / CT result refers to the tonsils "relatively symmetrical radiotracer capture in the palatal tonsils, without associated morphological changes" (Figure 3), and regarding the deep bilateral and lateral cervical submandibular ganglions it is found that "some have moderate FDG fixation, most likely of inflammatory etiology". Nothing was found in the rest of the body, and the conclusion of the PET-CT examination was "without metabolic injury". All these results were analyzed by the oncologist and the recommendation was of monitoring at 3 months.

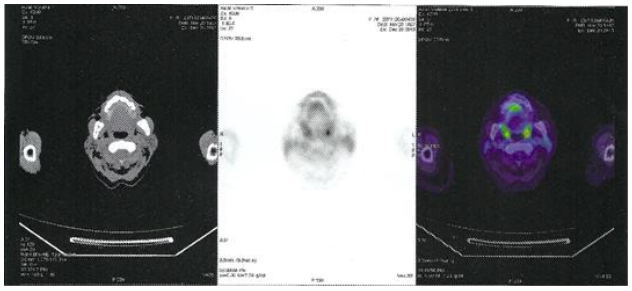

Figure 3 – PET-CT – relatively symmetrical capture of the radio transmitter at the level of the tonsils

In March 2014, the ENT specialist noted "No neoplastic signs of ENT level. No cervical adenopathy is felt" and this clinical situation was kept in 2015 until the last control in April 2016 when it was decided that patient be re-evaluated in 6 months. In parallel, the patient also presented to the oncologist. During this period there was a Mammography in 2014, X-ray examinations in 2014, 2015 and 2016, Abdominal and cervical ultrasound in 2014 and 2015. The examinations did not reveal any suspected tumor formation or adenopathy. Also, the annual analyzes were performed, which did not report anything special, and the tumor marker SCC was within normal limits.

On July 1, 2016, 3 years after the excision of adenopathy, the annual ultrasound examination revealed "left para internal jugular vein voluminous adenopathy, with tumor aspect, with diameters between 8/4 mm and 23/13mm,

some with necrosis aspect"; abdominal ultrasound was "without adenopathy or pathological masses detectable ultrasound". Cervical region MRI examination confirms "a necrotic tumor formation that develops at the level of the left palatal tonsil and has an approximate maximum diameter of 2/1.9/3 cm; the lesion spreads to the parapharyngeal space, reaching to the immediate vicinity of the left internal carotid artery; multiple images of left lateral cervical adenopathy appear, located in practically all ganglionic groups with maximum diameters up to 2.8 cm; Conclusion of oncological evolution was that "the present aspect advocates for a left palatine tonsil tumor with lymph node metastases" (Figure 4). Several successive ENT examinations conclude "Clinically without signs of ENT tumor; left submandibular adenopathy with firm consistency, hypomobile with slightly progressive growth within 6-7 months".

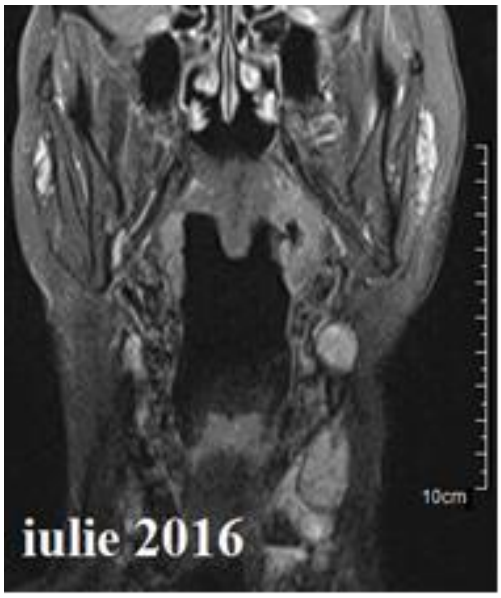

Figure 4 – Cervical MRI – left palatal tonsil tumor with left necrosis lateral cervical adenopathy

For the imaging diagnosis based on the conclusion of the MRI examination, a radiotherapist was first consulted, who considered "either radical surgery or biopsy in the left amygdala", considering that the radiation therapy has a prognosis reserved mainly due to the approach of the internal carotid tumor. An OMF surgeon was also consulted who specified that "the patient may benefit from radical surgical treatment (left radical neck dissection + tumor ablation by mandibulectomy + osteosynthesis) after investigations to confirm that the 79-year-old patient can support the operation; after the operation the patient had to be fed by PEG for a period of time or as an alternative to the surgical treatment to apply a treatment by chemoradiotherapy". Then, another radiotherapist was consulted in a specialized clinic and the commission of that clinic proposed "induction chemotherapy + definitive radiotherapy + radiosensitization chemotherapy + application of a PORT and PEG system".

In view of the complications of the proposed treatments regarding the quality of life, the risks due to both the age (79 years) and the position of the tumor relative to the internal carotid, the patient refused the left palatine tonsil biopsy and the proposed treatment schemes, opting for alternative treatments. The periodic ENT examination revealed a slow continuation of loco-regional evolution, with the appearance of the trismus and the infiltration of the lateral cervical tegument with permeation nodules. Cervical facial pain was moderate and did not require opioids. In July 2018, the ENT examination records "Neoplasm left palatine tonsil with left lateral cervical adenopathy in loco-regional evolution; left Collet-Sicard tumor syndrome, left peripheral facial palsy; left submandibular permeation nodules" (Figure 5). The evolution was unfavorable, with exitus at 5 years and 2 months after the diagnosis of metastatic cervical adenopathy, at the age of 81 years, of which 4 years and 7 months with good quality of life and the last 5 months in which the quality of her life has been degraded mainly due to dysphagia.

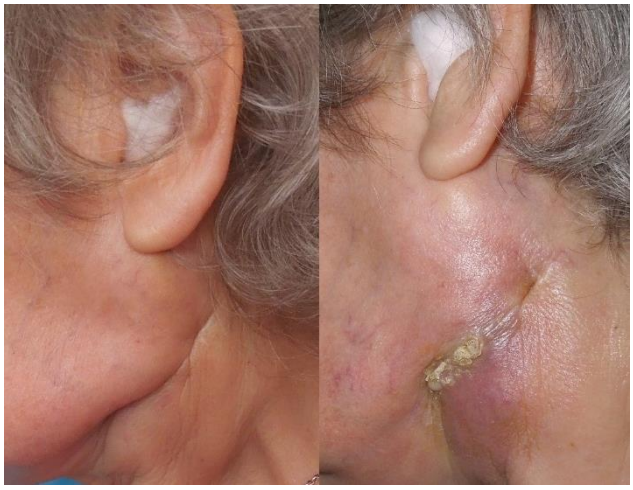

Figure 5 – Adenopathy exteriorized to teguments with permeation nodules

Discussions

It is known that the main risk factors in palatal tonsil cancer are smoking, alcohol, Papillomavirus infection, diet, exposure to pollutants (radon, asbestos). Regarding the diet it has been found that poor diets in protein, fresh fruits and vegetables, foods preserved by drying, salting or smoking increase the risk of oropharyngeal cancer [6, 7]. It should be noted that our patient did not have any of the risk factors listed above.

Di Maio P, Iocca O, De Virgilio A., et al, published a meta-analysis in 2018, regarding the efficacy of tonsillectomy in the diagnosis of squamous cell carcinoma of occult origin in the head and neck. The results of the PET / PET-CT scan on the tonsil chamber should always be confirmed by tonsillectomy. Thus, out of 25 patients who were scanned with PET-CT only 3 of them had unilateral tonsillectomy, but after undergoing bilateral tonsillectomy, 6 cases of squamous cell carcinoma were found in bilateral tonsil [8]. Other authors note that some malignant tonsils had normal FDG uptake; therefore, PET / PET-CT should not be used to exclude tonsillar cancer [9]. Performing blind biopsies on tonsils, instead of tonsillectomy, seems unreasonable and unjustified, considering that in 224 biopsies the existence of malignancy was confirmed in 11 cases, while in 126 cases of tonsillectomy it was confirmed in 48 cases. The results of systematic literature review suggest that tonsillectomy has a high overall rate of detection of subclinical primary tumors. Given the significant number of bilateral/contralateral occult tonsil tumors reported in the specialty literature, bilateral tonsillectomy should be considered in establishing the diagnosis of squamous cell carcinoma patients of unknown primary origin in the head and neck [8,9].

A rarer form was presented in 1972 by C. Micheau, Y. Cachin and et al on 6 cases, with solitary cervical lymph node metastasis, with a particular appearance, long time before the origin of the tonsil tumor becomes evident (one case after 1 year, three cases after 3 years, one case after 11 years). In the sixth case, the ENT physician examined the palatine tonsil region of the patient again, because the particular appearance of the metastasis after biopsy was similar to the cervical metastases from the other five patients. Although the clinical appearance did not show any pathological change, a tonsil biopsy was performed and a carcinoma was discovered. The particular aspect of the metastases found in these cases was that they were found in the sub digastric area, they were round, regular and mobile, with no clinical signs of malignancy, and the general pattern of the structure suggested a branchial cyst with malignant transformation. The authors considered that these cases present a special clinic and pathological form of great interest, as it gives the possibility of finding the primary tumor in the clinical latency phase and, implicitly, the treatment of the primary tumor and the metastasis at the same time as the improvement of the survival rate [10].

The clinical model with cystic lymph node metastasis with palatine tonsil starting point also applies to the clinical case presented by us. The solution proposed by C. Micheau, Y. Cachin et al. for a patient with a single cystic metastasis is radiotherapy including nasopharynx, amygdala lobe and tongue base. Thus, it is considered that the primary tumor will not appear at a later date, and the survival rate could be greatly improved [10]. Adjuvant radiotherapy that includes in the field of irradiation the most likely sites of occult primary tumor is recommended by several authors.

Unfortunately, in the case we are presenting, no tonsil biopsy was taken at the time of detection of left lateral cervical lymph node metastasis and MRI evaluation at 6 months intervals would probably have been useful. Also, adjuvant radiotherapy with inclusion of the left amygdala lodge in the irradiation field would have had a chance of stopping the evolution of the disease. Perhaps the lack of firmness in formulating the diagnosis and the therapeutic indication, as well as the discordant therapeutic indications and the age, contributed to the patient's decision to renounce the classic oncological treatment.

Conclusion

Cervical lymph node metastasis with unknown primary tumor remains a difficult topic for head and neck oncology. Most diagnostic and treatment protocols recommend unilateral or

bilateral tonsillectomy, with an increased chance of finding an occult tumor in the palatine tonsil, unilateral or bilateral tonsils. In the presence of a cystic cervical lymph node metastasis, the palatine tonsil should be the first location considered as the primary tumor site. Adjuvant radiotherapy must necessarily include in the field of irradiation and the tonsillar lodge, thus increasing the chances of loco-regional control of the disease and improving the survival rate at 5 years with a good quality of life. The side effects of oncologic therapy should be presented realistically to facilitate the patient's correct decision.

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Conflict of interests: The authors declare no conflict of interests.

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