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Abstract: Background. The risk of metastasizing in axillary lymph node is occasional in the head and neck cancers. This pattern of spread is difficult to explain and totally unpredictable even for these lymphophilic cancers.

Observation. A 72-year-old patient benefited, 11 years ago, of surgical oncology care associated with adjuvant radiotherapy for squamous cell carcinoma of the left floor of the mouth (pT4 pN2b M0). He presented a second primary malignancy at the right oropharyngeal level. Pet CT revealed a right infraclinic axillary metastasis. The metastatic origin was confirmed by pathological analysis.

Discussion. The current management of head and neck cancers is based on the histological pattern of infiltration, the size of the primary tumor and the pattern of metastasizing lymph nodes and potential distant spreading. Current tests allow us to diagnose most distant metastases even outside the usual area of lymphatic drainage. Involvement of axillary lymph node, probably through retrograde lymphatic spreading is not so rare in recurrences of oropharyngeal cancer (T3 - T4, N2, ...) as we have observed in the literature. In this review, we raise some degree of similarity between such oncological progression and factors related to this aberrant spreading.

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CASE REPORT

« Axillary lymph node metastasis in second oropharyngeal cancer»

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Introduction.

The treatment of squamous cell carcinomas of the head and neck, and their metastases, depends mainly on the stage of metastasis in the lymph nodes but also on the histologic stage of the primary tumor site (1,2). Lymphatic spread extends predominantly in the cervical region along certain specific drainage pathways to the clavicle, but this spread extends occasionally and unpredictably in the axilla, and even in the inguinal hollow in some extreme cases, as documented in the literature (3,4). The risk of hematogenous spread is low, less than 10%, with a predilection for the lungs, liver, bones, and even the skin, the limb muscles, etc. (3,4). The literature shows us that the rare cases of metastatic spread in the axillary lymph nodes occur in patients whose lymphatic drainage channels have previously been significantly altered, either by a lymphadenectomy, a radiation therapy, tumor recurrence or a combination of these different factors (5). Very few publications describe an axillary metastatic spread of cancers of the head and neck (1,3,5,6). Here, we report the history of a patient, aged 72 years, who presented with axillary metastatic adenopathy following a second oropharyngeal localization of squamous cell carcinoma.

Case.

A 72-year-old patient presented with a squamous cell carcinoma of the right tonsillar fossa, 11 years after treatment of a first squamous cell carcinoma of the left buccal floor.
The patient had permanently ceased his consumption of alcohol and tobacco (> 35 pack-years) upon his first cancer diagnosis. He had no personal history other than the squamous cell carcinoma of the left anterolateral buccal floor, for which he had received a left anterior pelviglossectomy, with a selective-type (levels I to IV) left neck dissection and right jugulo-omohyoid lymphadenectomy (levels I to III), staged pT4 pN2b M0, followed by adjuvant radiation therapy at 64 Gys on all of the surgical field up to left level V. A supplementary dose up to 70 Gys had been delivered on zone IV and in the left subclavian region following the discovery of a suspicious adenopathy in the tracking computed tomography (CT).
The reason for consultation, 11 years later, was a lateralized pharyngeal pain on the right side present for 3 months, accompanied by a homolateral intermittent otalgia, a dysphagia, a deterioration of general state, and a moderate weight loss (4.5 kg). The clinical examination revealed trismus, induration of the tonsillar fossa, and a 3 cm ulceration of the glossotonsillar sulcus on the right side. A right subangular mandibular adenopathy (Ib) was scanned. The panendoscopy and the magnetic resonance imaging (MRI) showed an infiltrative lesion on the right tonsil, from the hemitongue passing over the median raphe, more than 4 cm at the long axis, and an adenomegaly of 10 mm at the long axis at the right level 1b. The PET scan showed a sizable hypermetabolic right oropharyngeal lesion (SUV max: 15.9) encompassing a part of level Ib and a hypermetabolic right axillary lymphadenopathy of 6 cm at the long axis (SUV max: 12.5). Oropharyngeal biopsy revealed a second moderately differentiated squamous cell carcinoma and excisional biopsy of the right axillary lymph node showed metastasis of a squamous cell carcinoma similar and largely cystic in appearance. A thoracoabdominal CT did not show any primary lesion. For this second localization of squamous cell carcinoma, staged cT4 cN1 cM1, the patient received a gastrostomy and was treated by 6 courses of cisplatin- and 5-fluorouracil-based chemotherapy, followed by targeted maintenance therapy with cetuximab. The oropharyngeal lesion was stabilized and no other lesions were identified in the

cervicothoracic CT examination 18 months later.

Figures.
A, B : Hypermetabolic lesion in the right tonsil(A) and the right axilla (B) in PET-scan.
C, D : Microscopics views of squamous cell carcinoma in the right tonsil (Hematoxyline and eosine coloration). Nuclear atypia and abnormal mitosis in high power field (mark) and lack keratinization.
E, F : Axillary metastatic lymphadenopathy. Cystic tumor aspect of metastasis in low power field and similar cytological view of tonsillar tumor in high power field.

Discussion.

Metastasis to the axilla as described in our clinical case is not very rare, as shown by several studies on autopsies of people with head and neck cancer, where up to 2-9% of axillary metastases are found (1,2), and up to 57% in one study (6). It is likely that these figures are underestimated because even during an autopsy, these lymph nodes are not routinely dissected, especially if the lesions are subclinical (7). In clinical practice, the risk of distant metastases in head and neck cancers is < 10%. The most frequent localizations of distant metastases of squamous cell carcinomas of the head and neck in post-mortem studies are the lungs (66%), bones (22%), liver (10%), skin (1-2%), mediastinum and bone marrow. They are primarily attributable to hematogenous spread (3).
The cephalic lymphatic drainage system consists of 2 subsystems draining a flow of intercellular lymph towards a venous return. The superficial system is itself composed of different lymph node groups (parotid, facial, occipital, external jugular vein, etc.) draining mainly skin and subcutaneous tissues, typically to the fascia superficialis. The deep system corresponds to deep or terminal lymph node groups moving directly toward the internal jugular vein. They drain a portion of the lymph originating from the deep lymphatic system buried under the fascia superficialis and the drainage territories of adjacent organs, which allows for a relatively strong prognosis of the lymph node groups involved based on the starting location, size, and histologic status of the lesion. There are variable (possible anatomical variations) and complex interconnections between these 2 subsystems of the head and neck region but also indirectly with other systems originating between the lungs and the thorax (1, 5). Together, this means a drainage system organized in the form of a network.
Any obstruction in this network (surgical resection, compression, radiation therapy, tumor, or metastasis itself) can change this cascade of drainage (fibrosis, sclerosis, and lymphedema), and thus change the direction of the jugulo-subclavian lymph flow (1,6,8) promoting the development of collaterals (7). Some lymphographic studies have shown that the axilla becomes the main drainage area of the lateral and anterior cervical region after a radical neck dissection or after exclusive radiation therapy in this area (8). Rouvière was the first to demonstrate a retrograde flow and aberrant communication between the axilla and the lower cervical region in 1938 (8). According to his treatise on anatomy, this deep drainage can follow the efferent lymphatic pathway, passing by the transverse cervical, inferior jugular, or spinal accessory chains, then by the subclavian lymph node group to finally rejoin the central axillary lymph node chain by retrograde flow (7,8). Even under normal conditions, without any treatment of the neck, this communication may appear (9). Finally, a direct continuity can exist between the fat of cervical level V and the fat of the axilla (5).
According to Rouvière and Gray (6), another well-demonstrated explanation is the superficial cutaneous drainage system of the lower cervical and hemithoracic region towards the homolateral axilla.
In addition to these anatomical connections, in some cases, a lymphangiogenesis of tumoral origin also occurs (10). Finally, hematogenous spread stay possible by venous or even arterial network but in this type of spreading, usually we meet much lesions in the same vascular territory or even to distance and rarely an alone lesion (7).

Regarding the prognostic factors, regional lymph node status is the most important prognostic indicator. Survival is reduced by half with the presence of a single metastatic lymph node (2). It is thought that the rate of occult metastases in patients with cancers of the head and neck may be up to 20-25% (2,4). The risk of spread is directly related to the level of lymph node extension, with up to 10% of distant metastases if N1 and up to 30% if N2 or N3 or if there are > / = 3 lymph nodes (8). In theory, a lymph node metastasis beyond the clavicle or metastases in 2 or more cervical lymph nodes,

or a capsular rupture, or a hematogenous spread are indicators of poor prognosis in head and neck cancers (3,6,8). Local recurrence, venous infiltration, a stage 4 tumor, and regional evolution are criteria that increase the risk of distant metastases (2,3,6). This is also the case for an extensive infiltrative tumor of the soft tissue (T4), a tumor with a more aggressive histological type (including a poorly differentiated tumor), a perineural invasion, an angiolymphatic extension, or a lymph node metastasis with capsular rupture (3,4). The risk of spread increases exponentially with the thickness of the primary tumor (2,4).
There is also a well-demonstrated risk of axillary spread when there is cutaneous extension in the head and neck region, primarily in the anterior cervical region and especially in the presence of a tracheotomy/-ostomy(9). Similarly, the risk of axillary lymph node metastasis is higher with a lesion of the oropharynx or hypopharynx than with a neoplasia of the ear, the glottis, or the sinus. The prognosis also depends on the type of treatment carried out (6). Our patient had a tumor resection with adjuvant radiation therapy and he presented with a second localization. This is in accordance with the risk factors proposed by Koch (1).
In the literature, the time to detection for axillary lymph node metastasis of head and neck cancer is on average 17 months, ranging from 3 to 40 months (5). Axillary adenopathy may be detected clinically (60% sensitivity), by CT scan (< 90%) (7), by PET scan (75-93%), or by ultrasound. The diagnosis of metastasis is sometimes done by fine needle aspiration biopsy, sometimes ultrasound-guided (79% sensitivity but 100% specificity), and also by excision biopsy (2), as in our case where we opted directly for the excision biopsy given the significant size of the adenopathy and its accessibility.
Survival with axillary metastasis is 4.3 months on average and does not exceed 2 years in 90% of cases (6,7,8).
The differential diagnosis is not clear with a metastasis of breast carcinoma, neoplasia most often responsible for axillary metastasis, of lung cancer (3) or of upper esophagus or thyroid carcinoma especially if the lesion is unique (7). Another difficulty is the degree of reliability of the pathological diagnosis because there is no immunohistochemistry test to confirm the origin of a squamous cell carcinoma (7). In our patient, there are two arguments in favor of oropharyngeal carcinoma metastasis: first, no other primary lesion was identified by the CT or PET scan, particularly in the breast or lung, and secondly, the tumor has the same histological characteristics as the oropharyngeal tumor (7).
Some of the recommendations (standard of proof C) come up during a recurrence or a second localization of squamous cell carcinoma of the head and neck (7), if there is a cervical lymph node metastasis at level V (5), and whether or not the patient has had surgery or exclusive radiation therapy (7.9). In these situations, it seems reasonable to clinically examine the axilla at minimum (7), and some advocate carrying out a comprehensive clinical evaluation, especially of all lymph node areas. Similarly, if spread in unusual sites is diagnosed in the context of a recurrence of a carcinoma, it is recommended to search for distant metastases with a full clinical examination but also with thoracic and bone Imaging (CT, PET scan) or even liver and bone biology (6).

Ideal care in the presence of axillary adenopathy in head and neck cancer is still unknown, because very few cases and studies are currently available (7). There is no proof of effectiveness or recommendation concerning the indication of an axillary node dissection (8).
According to Kowalski (9), if the recurrence is localized at the axilla or in the superior mediastinum, this spread most likely represents an extension in contiguity of the disease and therefore a locoregional treatment seems most appropriate (9). If there is no other distant lesion and no sign of spread, a lymphadenectomy with associated adjuvant radiation therapy in the metastatic zone would seem preferable (6).

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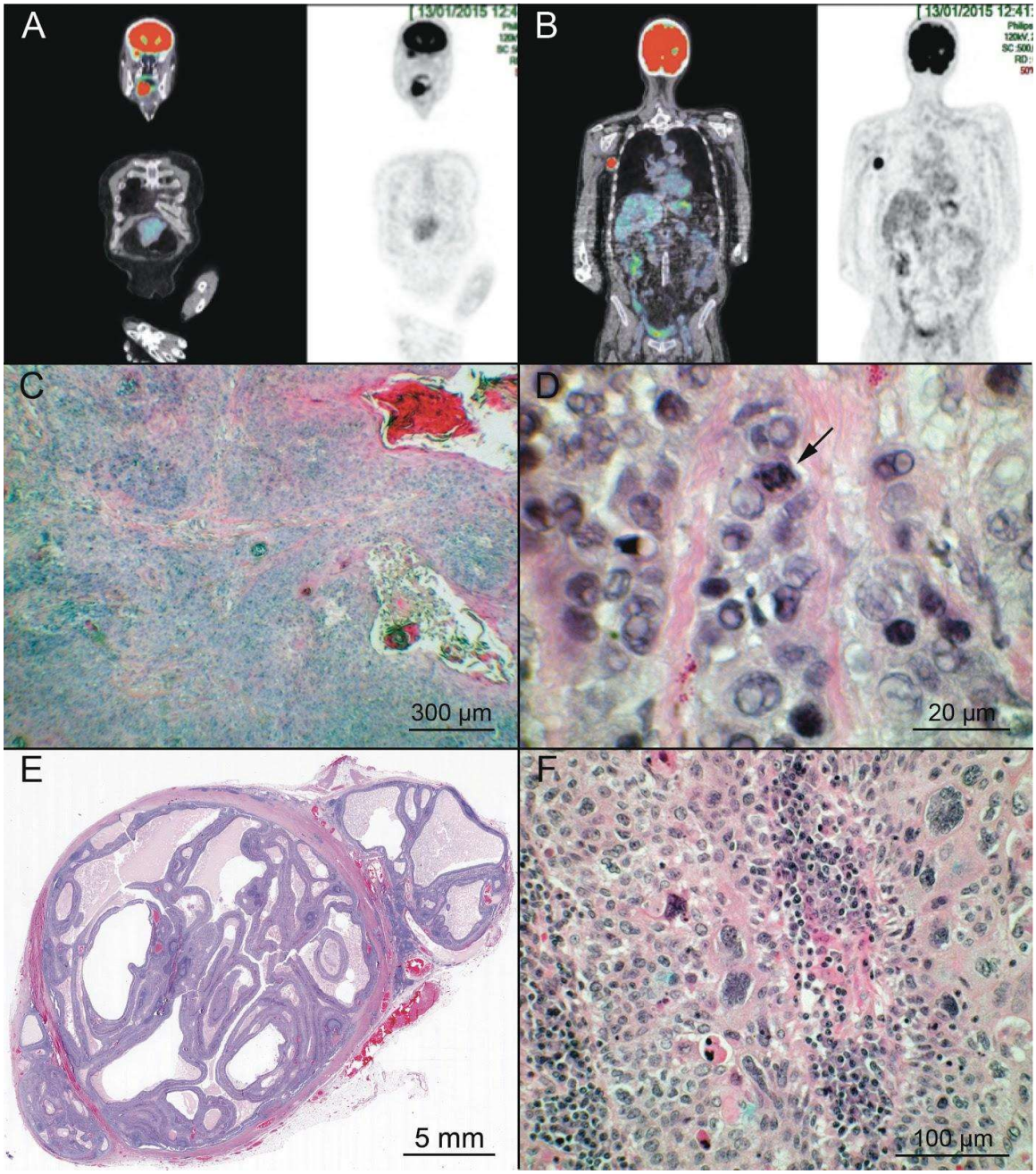
Figure



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