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Vascular emboli and perineural sheathing in cancer: a review of literature with evidence and prognostic value

Emboles vasculaires et engainement périnerveux par les cellules cancéreuses : une revue de la littérature avec évidence et valeur pronostique

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ABSTRACT

Vascular emboli and perineural sheathing in cancer are of great interest as they are considered as prognostic factors. But they are not often specified in anatomopathology reports. The authors review the literature.

RESUME

Les emboles vasculaires et les engainements périnerveux par les cellules cancéreuses dans le tissu tumoral sont parfois considérés comme ayant un intérêt pronostique. Ce dernier n'est pas toujours précisé dans les rapports d'anatomie pathologique ou d'imagerie médicale. Les auteurs présentent une revue de la littérature sur le sujet.

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Introduction

Vascular invasion and perineural sheathing are important histological and prognostic markers in cancer [1]. They are very common in breast, prostate, skin and urogenital cancers [2]. They are not always specified in pathology reports [1,2,3].

Literature review

State of the art

Tumor vascular emboli are defined as the presence of tumor cells within vascular structures outside the tumor. Their incidence varies according to tumor type, ranging from 20% to 95% [1,2]. Perineural sheathing (PNS) represents the invasion of the nerve by tumor cells, with one or more nerve layers affected. It was first described by Cruveilhier in 1835, and later in 1862, Neumann made the first description of PNS in skin cancer [3,4]. PNSs are most frequent in cutaneous squamous cell carcinomas (SCC) of the head and neck; in recurrent SCC, where their incidence varies between 2.4% and 14%, and up to 24%. [5,6]. These lesions are not often specified in anatomopathology reports, yet they are used as factors in local tumour recurrence and help to make the best management decisions [5].

Vascular emboli and perineural sheaths on imaging

Few studies have described the role of imaging in vascular emboli and perineural sheathing. Vascular emboli were less well described than perineural sheathing on imaging. The two imaging modalities most frequently described as enabling identification of these markers are computed tomography (CT) and magnetic resonance imaging (MRI) of tumors. In parotid tumors, it has been described that MRI plays a key role in the delineation of macroscopic tumor volume: T1-weighting enables the study of tumor boundaries and deep extensions. The T1 sequence, after injection of gadolinum and suppression of the fat signal, enables the study of perineural infiltration, bone or meningeal extensions [17]. Another imaging modality for detecting perineural sheathing is the use of PET in conjunction with MRI or CT. A case study of a salivary gland tumor showed a cystic adenoid carcinoma on histology, with maxillary and inferior turbinate involvement, pT4aNOMO. There was extensive perineural sheathing of the V2 nerve. MRI is of fundamental importance in the initial assessment of this tumor, enabling precise characterization of local, perineural and nodal tumor extension. 18FDG PET plays a diagnostic role for lymph node extension and the search for metastases. Cystic adenoid carcinomas of the salivary glands could be an indication of choice for PET/MRI in the pre-therapeutic extension work-up. In a comparison of PET/MRI and PET/CT examinations in a case of cystic adenoid carcinoma, PET/CT showed extension to the maxillary sinus, inferior turbinate and limited non-metabolic perineural infiltration of the V2 nerve. Tumor delineation on PET/MRI was more precise and extensive. MRI revealed extensive perineural extension of the V2 nerve (as far as Gasser's node). Image quality was better in ENT and whole-body PET/MRI. Artifacts were present and equivalent in CT and MRI. This enabled the authors to conclude that PET/MRI described the locoregional extension of this cystic adenoid carcinoma much more accurately than PET/CT, with superior image quality in ENT and whole-body [18]. Another study of tumor perineural invasion in squamous cell carcinoma of the alar rim of the left nostril in a 69-year-old woman presenting with neuralgia and paresthesia of the right trigeminal nerve, revealed subcutaneous infiltration of both nasolabial folds on MRI, as well as contrast enhancement of both trigeminal nerves down to the cavernous sinuses, indicating perineural envelopment by tumour cells [19]. It is therefore understandable that these two imaging modalities are of definite interest, especially in tumors with a high frequency of vascular emboli and perineural sheathing. However, MRI is the most effective imaging modality for assessing extension and perineural sheathing in tumors.

Testing for vascular emboli and perineural sheathing in the laboratory

In the laboratory, the search for vascular emboli and perineural sheathing is carried out in three main stages. A clinical study: patient's age (young or old), TNM tumor stage must be specified, a macroscopic study of the tumor (size, diameter, sections for better quality peri-tumor sampling). This is followed by a histological study using a microscope with an objective of 40 or 100, which reveals the following criteria for true vascular invasion: the presence of a cluster of tumour cells with smooth edges conforming to the contours of the lympho-vascular space, frequent changes in morphology with more eosinophilic cytoplasm, and the presence of vascular and lymphatic cells adjacent to the largest vessels in the tumour [15]. Another method of analysis is immunohistochemistry, which has demonstrated the value of using markers to detect vascular and lymphatic emboli in primary ductal breast cancer [16].

Prognostic factors for vascular emboli

Vascular invasion in cancer depends on a number of factors: histological grade, depth of tumor invasion, patient age and tumor size. The higher the grade, the greater the likelihood of emboli or perineural sheathing. In some tumors, a young age was a poor prognostic factor. The higher the tumor stage, the greater the risk of finding vascular emboli in the tumor.

Diagnosis is made on the basis of clinical signs, histology and immunohistochemistry, which will make it possible to detect vascular emboli in, for

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example, 46% of cases of endometrial cancers [7,8]. In breast cancer, the presence of vascular emboli is a poor prognostic factor. Their presence has shown to be an independent risk factor in patients without lymph node invasion and favors distant metastases reducing survival rates. It is also a risk factor for local recurrence. In a study carried out in Marrakech, we noted 7 cases of vascular emboli (35%), in line with the literature. Their presence favours distant metastases and reduces the survival rate [11]. Another study carried out in Rabat on breast cancers revealed that tumor size, hormone receptor status and the presence of vascular emboli were found to be predictive of invasiveness in their study, which was consistent with several studies (13]. In stage pT1b bladder cancers, 41% were associated with lymphatic or vascular tumour emboli, with reduced survival in patients with vascular emboli as opposed to those without. Vascular emboli was considered a negative factor in overall survival.

Prognostic factors in perineural sheathing

PNS is present in 7-35% of cases and has been described as a histological factor of severity and therefore of poor prognosis in tumors. Diagnosis is difficult, but the main feature is the diameter of the sheathed nerve, which is essential in characterizing PNS. On histology, the microscopic characteristics of PNS observed are: nerve diameter, number of sheathed nerves per slice of tumor section, level of sheathed nerve (dermis, hypodermis), the location of the nerve, the presence or absence of intra-nerve invasion, and the percentage of the nerve circumference in contact with tumor cells. Its presence is associated with local and overall prognosis, and its place among the histological criteria for adjuvant treatment needs to be clarified. The higher the tumor grade, the greater the risk of finding PNSs in the tumor. In cutaneous squamous cell carcinoma (CSC), peri-neural sheathing is fairly common, accounting for around 9.4% of CSC cases in the study below. The number of PNS has a negative prognostic value, with at least 1 having a higher risk of local recurrence and later death [9,10]. In a study of 187 prostate cancer patients in 2023, PNS was present in 93 patients (49.7%). It was considered an independent risk factor for Extra Capsular Extension (ECE) on prostatectomy specimens, and associated with an increased risk of ECE. PNS provided better prediction of tumour stage and management of prostate cancer [14].

Reflection on the presence of both situations

The presence of perineural sheathing or vascular emboli on the pathology report should be specified in accordance with the latest recommendations for standardized clinical surveillance committees. At present, in more than half of all cases, this is not done by the pathologist [13]. The presence of these two markers is a poor prognostic factor, and their positivity in breast cancer, for example, is a risk factor for regional lymph node invasion, metastasis and local recurrence of invasive cancer, which must be taken into account in the indication for treatment [11,12]. This also has an impact on overall survival and on the indication for adjuvant treatment in intermediate and advanced stage breast cancer.

Conclusion

Vascular invasion and peri-neural sheathing are increasingly studied as markers for survival in cancer. Their presence on tumorectomy specimens is recognized as a poor prognostic factor. Increasingly found on tumorectomy specimens, they need to be specified on pathology reports to help improve patient management decisions.

Conflicts of interest: No conflict

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