

LES CARCINOMES BRONCHIQUES NEUROENDOCRINES A GRANDES CELLULES

1. Introduction

Dans la classification OMS actuelle les carcinomes neuroendocrines à grandes cellules (CNEGC) font partie des NNE bronchiques primitives de haut grade au même titre que les cancers bronchiques à petites cellules (CBPC). Il s'agit de tumeurs rares dont la fréquence est estimée à 3% environ des cancers bronchiques (23,24).

2. Le diagnostic anatomopathologique

Par définition, les CNEGC présentent **une morphologie neuroendocrine ou organoïde**, en travées ou en massifs, avec des rosettes et des plages de nécrose abondantes

Les CNEGC sont cependant différents des CBPC en raison de la grande taille de leurs cellules, avec un cytoplasme relativement abondant (de plus de 3 lymphocytes, soit plus de 20 microns), souvent polygonal, non vacuolisé et aux cadres nets. Le noyau possède une chromatine grossièrement granuleuse ou vésiculaire avec des nucléoles bien visibles, et on observe plus de 10 mitoses pour 2 mm².

Outre l'architecture neuroendocrine, le diagnostic de CNEGC nécessite obligatoirement **une confirmation du caractère neuroendocrine par immunohistochimie**. Au moins un des trois marqueurs neuroendocrines spécifiques doit être exprimé : chromogranine, synaptophysine, ou CD56. Les CNEGC expriment souvent plusieurs marqueurs NE, mais de façon moins intense et diffuse que les carcinoïdes (25–27). Si un seul de ces marqueurs est exprimé, il doit l'être de façon diffuse. Dans la mesure où 10-20% des CBNPC peuvent avoir une surexpression de marqueurs neuroendocrines, il est essentiel de ne demander ce marquage que lorsque la tumeur a une morphologie évocatrice de tumeur neuroendocrine (19).

Environ 70% des CNEGC expriment le TTF1. Ils n'expriment pas p40. Ils ont souvent une expression élevée de Ki67, en général entre 40 et 80% (28), sans que cela ne soit spécifique. Cependant, cela doit remettre en question un diagnostic de carcinoïde atypique.

Enfin, il peut exister une variante anatomopathologique qui est le CNEGC composite, par combinaison d'un CNEGC avec tout autre contingent carcinomateux non NE : adénocarcinome, carcinome épidermoïde, carcinome sarcomatoïde (au moins 10% de chaque contingent). Si un CNEGC est associé à un CPC (quel que soit le pourcentage de ce contingent), c'est le diagnostic de CPC composite qui doit être porté.

Le diagnostic des CNEGC est difficile, en particulier sur le plan cytologique, à partir d'une PTP ou d'une cytologie bronchique par exemple. Dans une étude réalisée en 1998, Travis *et al* évaluent la reproductibilité de la classification des NNE et montre que le CNEGC est la tumeur la moins bien diagnostiquée, probablement par sa rareté et son entrée plus récente dans la classification avec lecture anatomopathologique par des praticiens peu habitués à la pathologie thoracique (29). Bon nombre de CNEGC seront donc pris par défaut pour des carcinomes indifférenciés à grandes cellules, d'autres types de CBNPC ou un carcinoïde atypique sur une simple cytologie, voire une biopsie bronchique ou ganglionnaire de petite taille, comme cela a été démontré dans l'étude de Jacques Le Treut, dans laquelle 11 des 40 CNEGC ont été reclasés dont 9 en CPC après relecture par un panel de médecins anatomopathologistes (30) et dans l'étude du GFPC où 35% des CNEGC ont été reclasés après relecture en panel (21).

L'expression PD-L1 des CNEGC commence à être étudiée (10% à 25% selon les niveaux de *cut-off* utilisés) (20,22) ; sans que l'on sache pour l'instant si cette expression est prédictive d'une réponse à l'immunothérapie.

En biologie moléculaire, les biomarqueurs les plus fréquents des CBNPC semblent rares dans les CNEGC (31–33) : il y a, en général, peu de translocation *RET*, ou *ROS1* (16,17,32,34) et peu de mutations *EGFR* (moins de 1%) (33).

Récemment, plusieurs cas de CNEGC survenant chez des patients non-fumeurs et présentant un réarrangement de *ALK* ont été décrits. Ces cas ont répondu à des thérapies anti-*ALK*. Il faut noter cependant que dans l'ensemble de ces références, il n'y avait pas de relecture anatomopathologique centralisée (35–39).

Les CNEGC sont en fait un groupe très hétérogène de tumeurs comprenant des altérations génomiques de CBNPC et de CPC (40–44) avec plusieurs sous types en cours d'identification :

- Les CNEGC de type I présentent des altérations bialléliques de *TP53* et *STK11/KEAP1* comme les CBNPC, mais une expression transcriptomique forte du phénotype neuroendocrine (expression élevée des gènes *ASCL1* et *DLL3*, et une expression faible de *NOTCH*). Ces tumeurs sont généralement positives en IHC pour Rb.
- Les CNEGC de type II présentent des altérations bialléliques de *TP53* et *RB1*, comme les CPC, mais diffèrent de la plupart des CPC par une expression transcriptomique faible du phénotype neuroendocrine (expression faible de *ASCL1*, *DLL3* et forte de *NOTCH*). Ces tumeurs sont généralement négatives en immunohistochimie pour Rb (inactivation du gène *RB1* le plus souvent par mutation).
- Certains auteurs semblent identifier un troisième sous type « proche des carcinoïdes » : les CNEGC qui présentent des altérations de *MEN 1* et une charge mutationnelle basse.

Sur le plan thérapeutique, les CNEGC de type II (qui ont perdu l'expression de Rb en IHC en raison d'une mutation inactivatrice) sembleraient mieux répondre à la chimiothérapie de type CPC, tandis que les CNEGC de type I (qui ont gardé l'expression de Rb en IHC / sont porteurs du gène *RB1* sauvage) sont plus sensibles à la chimiothérapie de type CBNPC (45).

En raison du caractère exploratoire de ces études, la recherche de ces marqueurs (*TP53*, *RB1*, *KRAS*, *STK11*, *KEAP1* en biologie moléculaire et Rb en immunohistochimie) est conseillée en pratique sans être indispensable.

Il s'agit de tumeurs rares et de diagnostic difficile.

Dans la mesure du possible et si cela doit modifier la prise en charge thérapeutique, il est impératif d'obtenir un prélèvement histologique par biopsie pour la prise en charge des CNEGC avec lecture par un anatomopathologiste thoracique entraîné (46). En cas de difficulté diagnostique, un réseau de référence pour la relecture anatomopathologique des tumeurs endocrines (réseau TENpath) soutenu par l'INCa a été mis en place. Pour plus d'information, voir le site www.reseau-gte.org/tenpath.

Parce qu'ils peuvent orienter la prise en charge, il est conseillé de chercher l'expression de Rb en immunohistochimie, et/ou de rechercher *RB1/KRAS/STK11/KEAP1* en NGS.

Si le patient est non-fumeur, il est recommandé de rechercher *ALK* en IHC et de demander une recherche standard en biologie moléculaire, ainsi qu'une relecture anatomopathologique.

3. Présentation radio-clinique et pronostic

Les CNEGC ne présentent pas de spécificité clinique. Les patients sont fumeurs dans plus de 80% des cas. Comme dans les autres carcinomes bronchiques primitifs, il peut exister un syndrome paranéoplasique (syndrome de Lambert–Eaton, syndrome de Verner-Morrison, rétinopathie paranéoplasique, etc.). Leur localisation est plus souvent périphérique que proximale. L'évolution métastatique est habituelle avec localisations hépatiques, osseuses et cérébrales fréquentes (24,47).

Du fait de la rareté des CNEGC, il n'y a pas d'études épidémiologiques prospectives et nous disposons seulement de quelques vastes études rétrospectives de registres nationaux et de quelques plus petites séries. (47–50). Les études historiques ont comparé le pronostic et l'évolution des CNEGC avec les autres carcinomes indifférenciés. L'étude rétrospective d'Iyoda en 2000, portant sur 2070 résections pulmonaires dont 47 carcinomes indifférenciés à grandes cellules et 72 carcinomes à caractère neuroendocrine, retrouve un pronostic nettement plus mauvais pour les CNEGC. En outre, en analyse multivariée, le caractère neuroendocrine est un facteur pronostic négatif (51). En 2002, cette même équipe rapporte une nouvelle analyse avec un nombre de patients plus important et constate que le caractère neuroendocrine est un facteur pronostic indépendant au sein des

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