L'HYPERPLASIE NEUROENDOCRINE PULMONAIRE DIFFUSE IDIOPATHIQUE (DIPNECH)

1. Définition

Décrite dès les années 50, la DIPNECH est reconnue comme une réelle entité clinico-pathologique depuis les années 90 (6), et entre pour la première fois dans la classification OMS des tumeurs bronchiques en 1999, comme lésions pré-néoplasiques de tumeurs carcinoïdes.
Une hyperplasie des cellules neuroendocrines pulmonaires peut être observée soit de manière idiopathique (DIPNECH), soit secondaire (foyers infectieux, cancers, hypoxie chronique, pneumopathie interstitielle diffuse, exposition environnementale, et de nombreuses maladies pulmonaires chroniques) (8). On parle alors de NECH/*tumorlets* secondaires.
La DIPNECH est rare (moins de 200 cas décrits), l'histologie seule ne semble pas permettre de la différentier d'une hyperplasie de cellules neuroendocrines secondaire. C'est l'association de cette histologie aux caractéristiques cliniques, radiologiques, et fonctionnelles respiratoires du patient qui permet le diagnostic de DIPNECH. Une bronchiolite oblitérante constrictive est souvent décrite dans le cadre des DIPNECH symptomatiques. Elle semblerait correspondre aux conséquences inflammatoires de la prolifération cellulaire neuroendocrine. La biopsie pulmonaire chirurgicale est donc le prélèvement de référence pour décrire l'histologie.

2. Caractéristiques cliniques et fonctionnelles

Il s'agit le plus souvent de femmes (90% des cas), d'âge moyen (58 ans), sans pathologie pulmonaire chronique préexistante.
Les symptômes respiratoires précèdent le diagnostic depuis longtemps (5 à 10 ans) : toux (71%) le plus souvent non productive, dyspnée (63%), sifflements (25%).
L'EFR révèle fréquemment un syndrome obstructif (78%), restrictif rarement (13%), ou mixte (17%).
Ces ordres de grandeur ont été récemment confirmés dans une étude rétrospective analysant 78 patients, dont 33 présentaient des DIPNECH et 45 présentaient des hyperplasies neuroendocrines secondaires (NECH) ou des *tumorlets* secondaires(195). Dans cette étude de Sun, les DIPNECH étaient pour la plupart des patients non-fumeurs (75%), alors que parmi les NECH/tumorlets secondaires, il y avait environ 69% de patients fumeurs.

3. Caractéristiques radiologiques

Les nodules et micronodules pulmonaires, souvent bilatéraux, constituent les lésions principalement retrouvées (82%). Ils correspondent très probablement aux *tumorlets* (inférieur à 5 mm) et tumeurs carcinoïdes (5mm ou plus) associés à la DIPNECH.
Certains nodules peuvent être calcifiés (11%).
Les opacités en verre dépoli et un aspect de mosaïque perfusionnelle par trappage aérique sont fréquents (37%), et peuvent être mieux détectés par des coupes scannographiques en expiration. Cette mosaïque perfusionnelle s'explique par la vasoconstriction des aires en aval de l'obstruction bronchiolaire et la redistribution du débit sanguin sur les aires ventilées normalement.
Un épaississement des parois bronchique est également fréquent (20%).

4. Evolution

Si la majorité des patients ne semblent pas évolutifs sur le plan radiologique et fonctionnel, il est important de connaître les deux principaux risques des DIPNECH : l'évolution vers l'insuffisance respiratoire et l'évolution de tumeurs carcinoïdes.
L'OMS classe l'hyperplasie neurendocrine pulmonaire diffuse idiopathique comme une lésion prénéoplasique. Elle est parfois associée à des tumeurs, bien différenciées et de bon pronostic (cT1N0M0 dans 95% des cas).
Trois études rétrospectives récentes ont souligné l'utilité d'une surveillance prolongée. Dans l'étude de Sun sus citée, sur 33 patients avec une DIPNECH, 9 (soit plus d'un quart) ont des nodules progressifs dont la résection révèle principalement des tumeurs carcinoïdes typiques (85%). Le temps médian de progression était estimé à 3,3 ans mais avec un intervalle large allant de 1 à 7,6 ans, pour un taux moyen de croissance de 0,8 mm par années. A noter dans cette série, 65% de positivité de l'IRS et 3 syndromes carcinoïdes. Dans une autre étude française, les patients avec une DIPNECH prouvée histologiquement étaient suivis(196). Sur les 27 patients suivis, avec un délai médian de suivi de plus de 5 ans, on retrouvait une augmentation de la taille des nodules pour 70% des patients et l'apparition de métastases chez 3 patients (11%). Le délai d'apparition de métastase était de 14, 70 et 123 mois. La surveillance scannographique de ces patients doit donc être régulière et très prolongée. Enfin dans une série anglaise (197) de 311 TNE bronchiques opérées, 61 (20%) avaient une DIPNECH histologique. La moitié de ces patients étaient asymptomatiques. 77% avaient des CT, 13% CA, et 10% les deux. 11% développent des métastases avec un délai médian de 37 mois. Les images et la fonction respiratoire restent le plus souvent stable ou s'aggravent très progressivement(198).
Le pronostic des DIPNECH est dominé par l'évolution de la fonction respiratoire. Le déclin de la fonction respiratoire est parfois rapidement observé (fibrose avancée et rapide). La source des décès des DIPNECH est respiratoire dans 4% des cas.
Il n'y a pas eu de description de DIPNECH associée au développement d'une néoplasie bronchique neuroendocrine de haut grade comme les carcinomes neuroendocrines à grande cellule et les carcinomes à petites cellules.

Recommandations

Il n'y a pas de traitement standardisé des DIPNECH.
Les tumeurs carcinoïdes associées aux DIPNECH doivent être prise en charge par résection chirurgicale anatomique en l'absence de contre-indication, avec si possible une stratégie d'épargne de parenchyme pulmonaire en cas d'atteinte multiple (60%).
La surveillance scannographique et fonctionnelle de ces patients doit être très régulière et prolongée, comparée à l'imagerie initiale, et supérieure à 10 ans.

La qualité de vie de certains patients peut être très altérée par l'importance des symptômes, en particulier de la toux. Dans une étude rétrospective réalisée au sein de 3 centres, l'utilisation d'ASM sur 42 patients porteurs de DIPNECH a permis une amélioration à la fois des symptômes (dans 76% des cas, mais jugée comme significative dans seulement 25% de ces 42 patients traités) mais aussi de la fonction respiratoire (86% jugée comme légère) (199). Néanmoins, ce médicament n'a pas d'AMM dans cette indication et les effets secondaires doivent être mis en balance du bénéfice attendu sur la qualité de vie. Dans cette étude, on relève rétrospectivement 38% d'effets secondaires : malabsorption, ballonnement, diarrhées, fatigue, hyperglycémie, lithiase biliaire.

OPTION : l'utilisation d'analogue de somatostatine hors AMM à visée symptomatique pour contrôler les symptômes respiratoires des cas sévères de DIPNECH doit être discutée au sein des RCP de référence RENATEN. Au vu des effets secondaires possibles, le maintien de ce traitement doit être sous-tendu par une amélioration clinique et/ou fonctionnelle significative. Aucun bénéfice sur la survie de ces patients n'est à ce jour prouvé.

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