新潟県厚生連医誌 Niigata-Ken Koseiren Med J, nkmj928,
T. Ikarashi, accept 2024/5/3, release 2025/01/27, vol. 34.

Invention report

Application of comprehensive genomic profiling (CGP) test to an identification of primary organ in cancer of primary unknown (CUP) - Reassessment of the significance of the staff requirement for multiple pathologists in the CGP test and expert panel –

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Key words: cancer of unknown primary (CUP), identification of primary organ, comprehensive genomic profiling (CGP), pathologic genetic variant, expert panel, FoundationOne™ CDx (© Roche, Chugai Pharmaceutical Co.), OncoGuide ™ NCC oncopanel system (V3) (©Riken Genesis, Kawasaki Laboratory), COSMIC registration (Catalogue of somatic mutations in cancer, NPO Wellcome Sanger Institute), Japanese version of the Cancer Genome Atlas (JCGA, Prefectural Shizuoka Cancer Center,

https;//www.jcga-scc,jp/ja, Graphs showing the relationship between pathologic genetic variants and preferred primary organs), COSMIC registration (Catalogue of somatic mutations in cancer, NPO Wellcome Sanger Institute)

Conventional methods to determine the primary site of cancer are based on the following three approaches:

1. tumor size at the time of discovery and characteristics of invasion and metastasis,

2. imaging studies,

3. histopathology and immunochemistry.

Recently the pattern of genetic variants is useful to presume the primary origin of cancer. Naomi Lynn Ferguson, one of resident pathologists at Foundation Medicine, stated in her CGP "F1-CDx" lecture, “If our genetic result is inconsistent with the client’s diagnosis, one will be instructed to review one’s original diagnosis.” OncoGuide ™ NCC oncopanel report, furthermore, lists the genetic variant frequency of the primary organ in each detected genetic variant based on COSMIC registration, and there are several reports that it is possible to narrow down the primary site in cancer of

unknown primary based on CGP statistics of the relationship between pathologic genetic variants and preferred primary organs.

On the process of CGP analysis the identification of candidate drugs against cancer of unknown primary have been discussed at an expert panel meeting, but the analysis of its primary site has not been discussed in detail.

In this report we reported on our study to narrow down the primary site based on the results of pathologic genetic variants: the example case was a case of "adenocarcinoma" of unknown primary, with multiple tumor foci throughout the body, and had six pathologic genetic variants (BRAF, SMAD, PBRM1, CDKN2A, MPL, STK11), microsatellite instability stable (MSS), and tumor mutational burden high (TMB-H) 16.6 on the CGP test. Referring to the diagram of the association of preferred primary organ frequency for each pathologic genetic variant listed in the Japanese version of the Cancer Genome Atlas (JCGA), the organs showing all above 6 genetic variants were endometrium, colon, stomach, and lung. The partially matched organ was the rectum. Once the primary sites are narrowed down to several ones, the primary site can be finally estimated by an additional immunohistochemical examination. Although the above method to confirm primary organ cannot guarantee absolute precision, it is

worthwhile to apply the CGP test to molecular pathological search for the primary organ.

We believe that the expert panel meeting after CGP test provides a patient the opportunity for the therapeutic trials with unapproved molecularly targeted drugs. But, as mentioned above, it is very useful for molecular pathologists that this active participation searching for primary organ as one of post-test annotations. These complicated procedures of this post-test annotation followed with immunohistochemical study as well as a pre-test accuracy control of CGP test requires a large number of man-hours, which is why multiple pathologists are considered essential.

英文和訳

小さな工夫

原発不明癌の原発臓器特定への包括的がんゲノムプロファイリング（comprehensive genomic profiling, CGP）検査の応用　―CGP 検査エキスパートパネル開催要員要件における病理医が複数必要とされる意義の再評価―

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キーワード：原発不明癌、原発臓器の特定、包括的がんゲノムプロファイリング（comprehensive genomic profiling, CGP）検査、遺伝子変異、遺伝子バリアント、エキスパートパネル、F1-CDx（ロッシ、中外製薬)、NCC オンコパネル（理研)、COSMIC (NPO Wellcome Sanger)、日本版がんゲノムアトラス（JCGA、静岡がんセンター)、遺伝子バリアントと好発原発臓器との関連グラフ、

従来の癌の原発部位の確定方法は、発見時の腫瘍の大きさ、浸潤・転移の特徴、画像検査、病理組織・免疫組織検査に基づく。最近、原発不明癌の CGP 遺伝子検査による遺伝子変異が判明した後に、遺伝子別の好発臓器に関する統計に基づく原発巣の絞り込みが試みられている。そこで、遺伝子異常の結果に基づく原発病巣の絞り込みに関して検討したので報告する。

症例は全身に多数の腫瘍病巣を認める原発不明の「腺癌」症例で、CGP 検査上の pathological な遺伝子変異は 6 種（BRAF, SMAD, PBRM1, CDKN2A, MPL, STK11)、MSS, TMB-H 16.6 であった。日本版がんゲノムアトラス（Japanese version

of the Cancer Genome Atlas, JCGA)の好発臓器別遺伝子変異頻度グラフ上、上記全ての遺伝子変異を示す臓器は、子宮内膜、大腸、胃、肺であった。また、一部が一致する臓器は直腸であった。ここまで原発巣が絞り込めると、免疫組織学的検討を加えることにより原発部位を推定できる。

上記の方法では精確さは保証できないが、CGP 検査を原発巣検討の為の病理学的検索に応用することに意義を見出せる。

CGP 検査後のエキスパートパネル検討会は、一義的には治験に結びつけることによる患者サービスであるが、それに留まらず、事後の原発巣探求への分子病理学的応用として価値があると信じる。上記のように、CGP 検査の検査前精度管理のみでなく、検査後のアノテーションへの積極的参加には、作業工数が多くなり、複数名の病理医が必須とされる理由である。

(2024/05/04)

一部改定(2024/09/23)