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Case report

Case of comprehensive genomic profiling (CGP) examination: Importance of Molecular Pathological Review after CGP examination

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Background: There is a genomic medicine with molecular targeting drugs as a tailor-made treatment of a cancer. For the application of trials by molecular targeting therapy to cases resistant to standard treatments, CPG test is preceded, and Center for Cancer Genomics and Advanced Therapeutics (C-CAT) investigation report is discussed among experts in genomic medicine hospitals. Because the purpose of this examination puts too much importance in the possibility of clinical trials, there is the anxiety in the additional examination of molecular pathology about carginogenic mechanism and gene variation. This report discussed these anxieties through our case.

Case report: The female patient with advance gastric cancer received CGP test for the

trial of treatment with molecular targeting drugs after standard treatments. The report of F1CDx (Foundation One Co.) inspection revealed as follows: Microsatellite stable (MSS), Tumor mutational burden (TMB) low, three abnormality variation, and four variants of unknown significance. (VUS). There was, nevertheless, no chance of trials and no evidence of secondary findings on later C - CAT investigation report and expert panel discussion. We reexamined the gene variation from the portion of a molecular pathologist and showed that this case was EBV-positive subtype and loss of heterozygosity (LOH) in MLH6.

Conclusion: In expert panel discussion it is easy to end up with whether the genetic variants can reach a clinical trial or not, and disregard the investigation of molecular pathology.

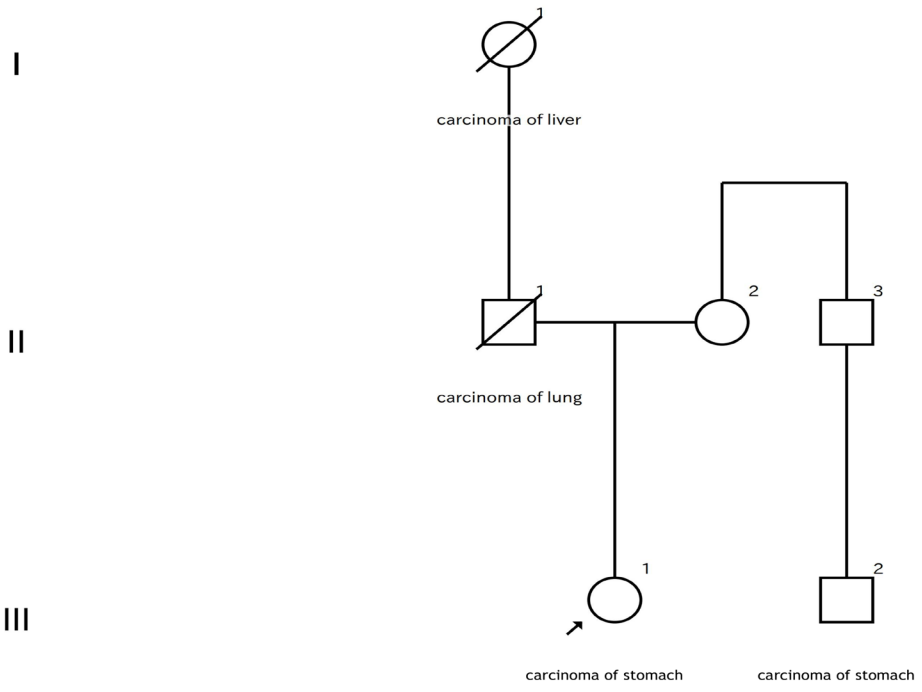
Key words: cancer genomic medicine, comprehensive genomic profiling test (CGP), expert panel, Center for Cancer Genomics and Advanced Therapeutics (C-CAT), certified molecular pathologist, molecular pathologic approach, bidirectional analysis between histopathological diagnosis and genomic variation, review of histopathology after expert panel, supplement of CGP results by additional polymerase chain reaction

test (PCR) and immunohistochemical analysis (IHC)

Case presentation

The case was 62 years old, female, affected with adenocarcinoma of gastric cancer, por2>tub1 and HER2 (-).

Family history as Figure,



Current medical history:

X-2 (year)/11 (month): distal gastrectomy was performed, post operative pathology: pT4aN3b p0 cy1 m1 (paraaortic lymph node), stage IV, postoperative chemotherapy (I) S-1, (II) SP (S-1+CDDP),

x-1/5: imaging revealed swelling of para-aortic node: assessed as progressive disease (PD) as effectiveness, (III) RAM+nabPTX partial response (PR), (IV) S-1,

X-1/11: PD, (IV) nivolumab PR,

X/4: PD, (V) CPT11 PR, (VI) nivolumab PR,

X/10 PD, (VI) TAS-118+RAM, at last CGP test was submitted,

CGP (F1CDx-H by Foundation Medicine/Chugai/Roche) report, and Center for Cancer Genomics and Advanced Therapeutics of National Cancer Center (C-CAT) investigation report revealed as follows: (1) Microsatellite instability: stable (MSS), (2) Tumor mutational burden (TMB) low 0, (3) ARID1A: variation rate=14.0%, evidence level=F, PIK3CA: 7.8%, C, RAD54L: 46.9%, -, TP53: 15.8%, F, (4) Variant of unknown significance (VUS): MSH6: 47.9%, A, PDGFRB: 45.9%, C, PIK3CG: 56.2%, -, SNCAIP: 7.3%, -

Results on Expert Panel Report:

There was no recommendations in domestic therapeutic trial,

Secondary findings: no variants to disclose.

Discussion

This patient had advanced gastric cancer, which had progressed after gastrectomy and 6 lines of adjuvant chemotherapy with molecular targeted drugs, and finally CGP test was performed to investigate the possibility of a clinical therapeutic trial by molecular targeting drugs. As for the result of CGP test, gene mutations consisted of 1. MSS, 2. TMB-L 0, 3. ARID1A: 14.0%, F, PIK3CA: 7.8%, C, RAD54L: 46.9%, -, TP53: 15.8%, F, and 4. VUS: MSH6: 47.9%, A, PDGFRB: 45.9%, C, PIK3CG: 56.2%, -, SNCAIP: 7.3%, -. There were no valid trials and no secondary findings in the expert panel.

This CGP study was discussed with respect to the following two points: (1) the lack of molecular pathologic carcinogenetic mechanism and histologic classification and

(2) the lack of effort to introduce clinical therapeutic trials. Participating in the expert panel held with Niigata University as the core facility as an observer for the last three years, only both the reachability of clinical therapeutic trials and the presence of secondary findings were emphasized after reading up the mutated genes in the C-CAT report. In fact, the present case was treated in a similar above manner on the expert panel. But just after registration as the collaborating hospital in the CGP system, we had the opportunity to peruse the F1CDx-Histology analytic report and C-CAT report of this our own case and reviewed: (1) the confirmation of the characteristic mutated gene pattern (PIK3CA 56.2%, ARID1A 14%) and microscopic reexamination for the presence of characteristic histological features; The central part of the tumor was desmoplastic adenocarcinoma due to ulcer scarring, but the surrounding scar-free area consisted of moderately differentiated adenocarcinoma with the high degree of lymphocytic infiltration. This lymphocytic reaction suggested Epstein-Barr virus (EBV) related malignancy. Furthermore, PCR testing at our institution confirmed EBV and allowed us to determine as the EBV-infected gastric cancer of the TGCA classification (The Cancer Genome Atlas Network Group Program, 2014). This subtype was reported as a strong immune involvement, which corresponded to the good reactivity of

nivolumab effect (PR). As for (2), the report considered 47.9% of MSH6 mutation frequency to be VUS, and although the C-CAT survey results showed an evidence level of A, it was judged to be difficult to reach the domestic clinical therapeutic trial. However, the 47.5% mutation frequency is clearly loss of heterozygosity (LOH) compared to the 30-50% tumor cell fraction in the specimen in spite of MSS and TMB-L, and there is still a possibility that pembrolizumab could be used by an insurance coverage as a companion diagnostics (CDx) after additional consideration of deficient mismatch repair (dMMR) with immunohistochemistry (IHC). Since I am now a certified pathologist instead of previous board-certified gynecologist specializing in gynecologic cancer, I have missed the opportunity to provide any informed consent (IC) directly to patients to undergo a genetic examination. The determination of dMMR through hospital-paid research IHC was easy and could lead the attending physician to implement the insurance-covered dMMR testing for molecular target therapy. The role of the molecular pathologist is not only to concentrate on the pre-analytical stage of a formalin fixation and an examination of tumor cell population for assuring the quality of samples, but also to reexamine the histopathology after the CGP test by further stepping to be in line with the recent WHO histology classification that is shifting the

emphasis to molecular pathology.

和文抄録

症例報告　Comprehensive Genomic Profiling (CGP)検査の 1 症例：CGP 検査後の分子病理学的再検討の重要性

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背景　癌治療のテーラーメイド治療として遺伝子検査・分子標的薬がある。癌の標準治療抵抗性の症例への分子標的薬治験提供の為に、がんゲノム医療の提供体制における CGP 検査・C-CAT 調査報告・エキスパートパネルによる検討がなされている。その検討目的が治験への到達性に偏重し、発癌機序・遺伝子変異の追加検査等の分子病理学的検討が十分になされない危惧があり、自験症例に関して再検討したので報告する。

症例内容　症例は進行性胃癌で、胃切除後 6 回の標準治療にもかかわらず傍大動脈リンパ節転移憎悪により治験目的で CGP 検査を受けた。組織 F1CDx 検査上、MSS,

TMB-L, 異常な遺伝子変異 3 個、VUS4 個が検出された。その後の C-CAT 調査結果に基づくエキスパートパネルレポートでは、有効な治験は無いとされた。分子病理専門医の立場で、判明した遺伝子変異から振り返って病理組織を再検討した：１．病理組織の再鏡検と EBV 検査より分子病理学的には hot な免疫機序を伴う TGCA 分類 EBV 陽性型で、２．VUS の MLH6 の LOH より追加検査・CDx の可能性が高いと判断した。

結論　今回の CGP 検討に関して、以下の２点を強調した：（１）症例ごとの分子病理学的な発癌機序と組織分類がなされていないこと、（２）CGP 検査後の治験や治療への追加検査の補完の努力不足を感じたことである。臨床医を主体とするエキスパートパネル検討において、治験への到達性が重視されやすく、分子病理学的な再検討がなされない傾向があり、より深い検討を望みたい。同様に、分子病理専門医に限らず、病理医はプレアナリシス段階でのホルマリン固定と腫瘍細胞割合の検討に専念するだけでなく、もう半歩踏み込んで CGP 検査結果判明後に病理組織像との対比精査することが、近年の WHO 組織分類の分子病理への重点を移す傾向と軌を一にする重要な義務であると思う。更に、自施設で可能な検査を指導追加することにより、より治療の到達性を上げることが可能であろう。

キーワード：がんゲノム医療、CGP 検査、エキスパートパネル、C-CAT 報告書、分子病理専門医、分子病理学的アプローチ、病理組織診断とゲノム変異の双方向的検討、エキスパートパネル結果に基づく病理組織の再検討、免疫組織化学及び PCR の追加検査による CGP 結果の補完