Case Report

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Case report of multiple primary cancers and results of genetic testing to preliminarily explore their pathogenesis

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Abstract

The occurrence of multiple primary malignancies in a single patient has been relatively rare. We report here the case of a 71-year-old man with three primary tumors of lung cancer, intrahepatic cholangiocarcinoma, and prostate cancer, and a preliminary study of the mechanisms by which multiple primary tumors develop at the genetic level. Because of the late stage of the patient's condition, large tumor burden, and poor physical status, the patient survived only a few months. In the case presented herein, cholangiocarcinoma, lung cancer, and prostate cancer were found simultaneously, and the pathogenic sites are not related. Whole-exome sequencing was performed on the pathological tissues to explore the mechanism that may underlie multiple primary cancers at the genetic level. Several gene mutations were found in this case. They involved cell proliferation, cell cycle regulation, genetic stability, metabolism, cell invasion, angiogenesis, cell apoptosis, and other pathways. It can be preliminarily inferred that the mechanism underlying multiple primary tumors is related to the abnormality of tumor-promoting and suppressing pathways.

Keywords

Genetic mutation, whole-exome sequencing, multiple primary cancer, case report

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Introduction

In recent years, the tumor detection rate has increased, and some patients are found to have multiple primary cancers (MPCs). MPCs often occur in the digestive, respiratory, and urinary systems.[1–4] The site of second primary cancer is closely related to the site of the first primary cancer, and the diagnosis is based on the standards established by Warren and Gates in 1932.[4] The most famous pathogenesis of MPC is the theory of field cancerization proposed by Slaughter et al. in 1953 to explain the development of head and neck squamous cell carcinoma, which is often accompanied by multiple malignant or precancerous lesions.[5]

There is no standard treatment plan or recommendation for MPCs; thus, treatment remains difficult. Treating tumors according to the type of gene mutation may provide a new direction for the diagnosis and treatment of MPCs. We here report, for the first time, a case of three primary tumors of lung cancer, intrahepatic cholangiocarcinoma, and prostate cancer, and a preliminary study of the mechanisms by which multiple primary tumors develop at the genetic level.

Case presentation

The patient, male, 71 years old, with a previous history of hypertension anamnesis, with no family history of cancer, was admitted to the hospital with "upper abdominal distension for 5 months, aggravated for half a month" on March 9, 2020. He

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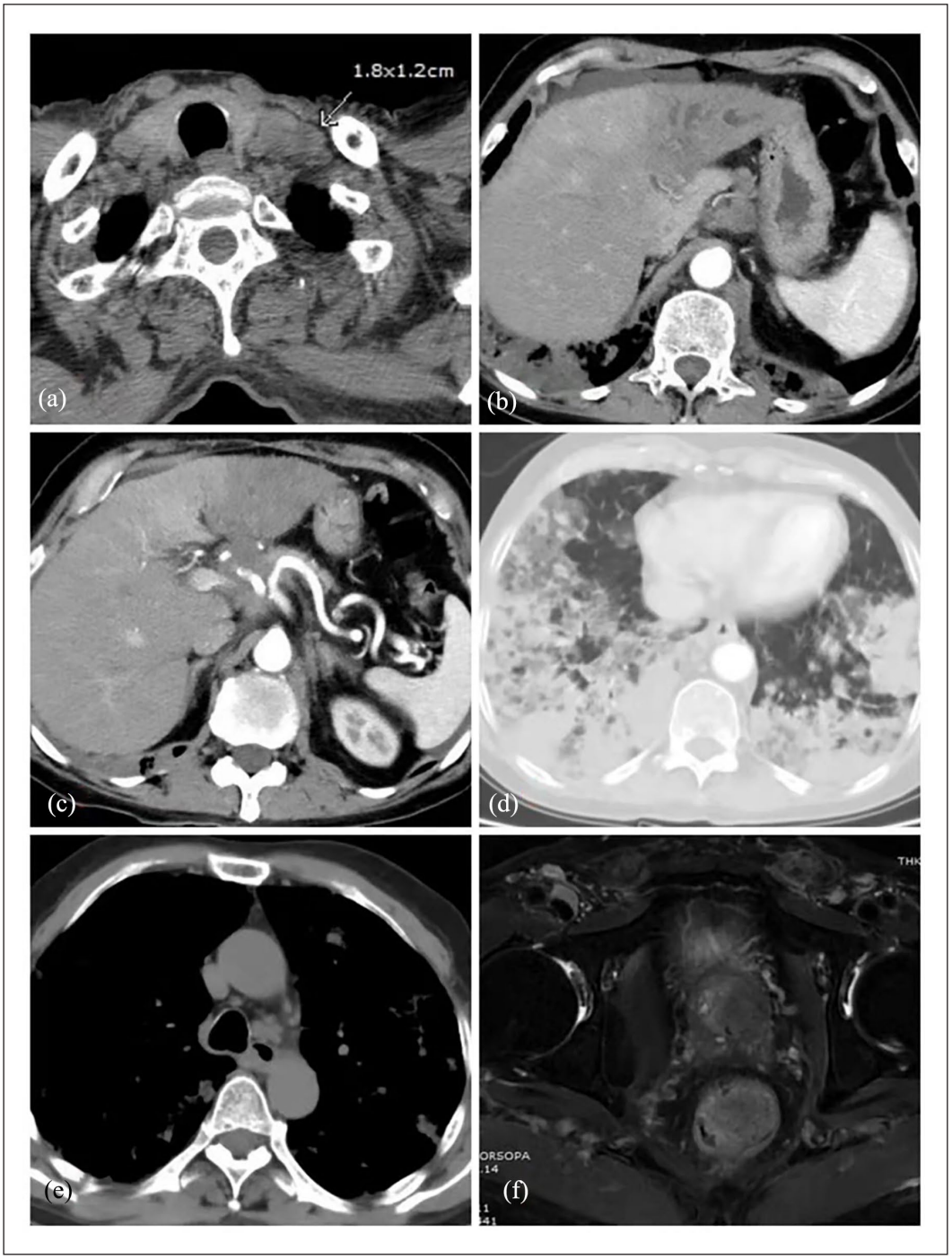

Figure 1. Chest and abdomen computed tomography and pelvic magnetic resonance imaging. (a). Left supraclavicular lymph node enlargement, diameter 1.8 × 1.2 cm. (b), (c). Left lobe of liver, low-density foci in hilar area, mild enhancement, unclear boundary with pancreatic head, hepatogastric space, abdominal cavity, retroperitoneal lymph node enlargement. (d), (e). Double lung patches, masses, and nodules of primary lung tumors and mediastinal lymph node enlargement. (f). Nodular abnormalities in the left posterior and anterior edges of the prostate, involving both sides of seminal vesicles.

had smoken 20 cigarettes a day for 20 years, drunk alcohol 200 ml a day for 10 years. Physical examination revealed palpable left supraclavicular 1.5 × 1.5-cm lymph nodes that were hard with no tenderness, unclear borders, and poor mobility. Wet rales sounds were audible in the right lower lung, and the lower edge of the liver was located 5 cm below the xiphoid process of the midline of the body. The right midclavicular line was 1 cm below the costal margin, which was tough and lightly tender. Results of blood tests upon admission to the hospital were as follows: SCC 6.24 ng/ml, CA50 > 500 IU/ml,

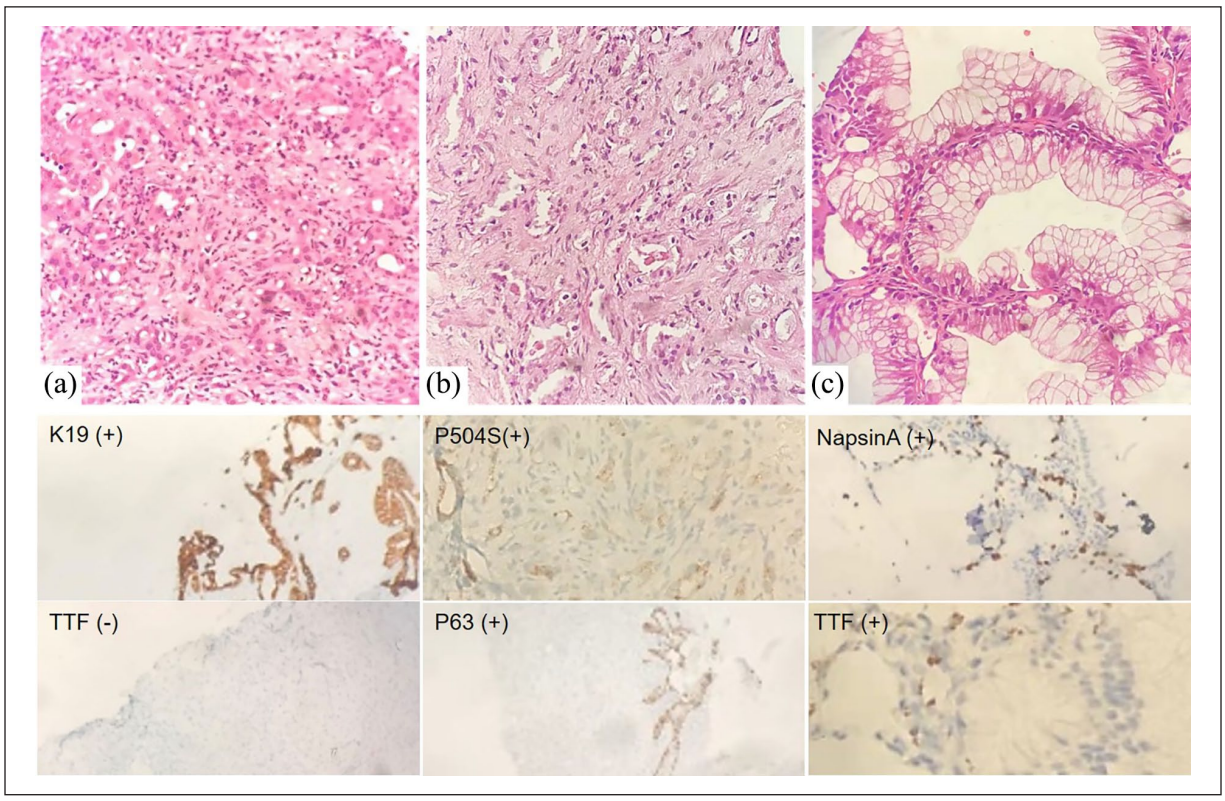

Figure 2. Pathological results of needle biopsy. (a). Liver mass biopsy pathology: adenocarcinoma indicative of intrahepatic cholangiocarcinoma combined with medical history and immunohistochemistry. Immunohistochemistry: hepatocyte (−), GPC-3 (−), CK19 (+), CK7 (+), TTF-1 (−), NapsinA (−). (b). Pathology of puncture of prostatic space-occupying lesions: (1–9 prostate punctures) acinar adenocarcinoma; overall Gleason grading score: 3 + 4 = 7 points; immunohistochemical results: P504S (+), P63 (basal cell-). (c). Pathology of pulmonary puncture biopsy: mucinous adenocarcinoma, combined with morphological and immunohistochemical results, consistent with the primary lung. Immunohistochemistry: CK20 (−), CK7 (+), CK19 (+), NapsinA (+), TTF-1 (+), Villin (−), SATB2 (−), PSA (−).

CA242 > 200 IU/ml, CEA 15.19 ng/ml, CA19-9 > 1000 U/ml, AFP 3.07 ng/ml, CA125 140.7 U/ml, TPSA 81.14 ng/ml, FPSA 7.363 ng/ml, FPSA/TPSA 0.09, NSE 17.76 ng/ml, and CYFRA21-1 10.76 ng/ml. Chest and abdomen computed tomography (CT) and pelvic magnetic resonance imaging results are shown in Figure 1. Tissue biopsy was performed in lung-, liver-, and prostate space-occupying positions, and the pathological results are shown in Figure 2.

A complete general check-up showed no metastasis to other organs. Diagnosis before treatment was as follows: 1. Intrahepatic cholangiocarcinoma cT4N1M1 stage IV invasion of pancreas, hepatogastric space, abdominal cavity, retroperitoneal swollen lymph node metastasis; 2. Lung mucinous adenocarcinoma cT4N3M1 stage IV left supraclavicular lymph node metastasis and lung metastasis; 3. Prostate cancer cT3bN0M0 stage III (UICC/AJCC TNM, 8th edition).

The patient's prostate tumor and intrahepatic cholangiocarcinoma biopsy tissues were tested via whole-exome sequencing (WES). The Integrated DNA Technologies (IDT) xGEN Exome panel consists of 429,826 biotinylated probes designed to capture 19,396 genes (a 39 Mb region). Then, 20 same mutation sites in 16 genes, such as *KMT2C, ANKS1A, ATAD3B, CABLES1, CHIT1, FAM155A, LCORL, MAFA, MKRN1, MUC17, MUC6, PRSS3, RBMX, RETSAT, SREBF2, and UBXN11* (Figure 3(a), Supplemental material Table S1) were found in both tissues. Besides, we selected four same peptides from the both tissues (Figure 3(b), Supplemental material Table S2). On the other side, due to the limited sample size, the lung tumor tissue was insufficient for WES, and was sequenced by a Next-Generation Sequencing (NGS) panel (A total of 23 gene variants were examined in this panel, covering all exon variants (including exon-intron interface regions) of 15 genes, partial exons of 8 genes, and partial introns of 12 genes.), and only *KRAS* was found to be mutated (p.G12V, Exon2).

We inferred from the patient's normal liver function that prostate cancer lesions were still limited. The lung lesions were extensive, and the patient showed hypo-immunity, so the patient's condition may have been complicated by intrapulmonary infection at any time. This would make lung cancer the most likely potential cause of death for this patient. The treatment plan considered three types of tumors by selecting docetaxel 60-mg i.v. drip d1, 2 + nedaplatin 60-mg i.v. drip d1, 2, combined with recombinant human endostatin

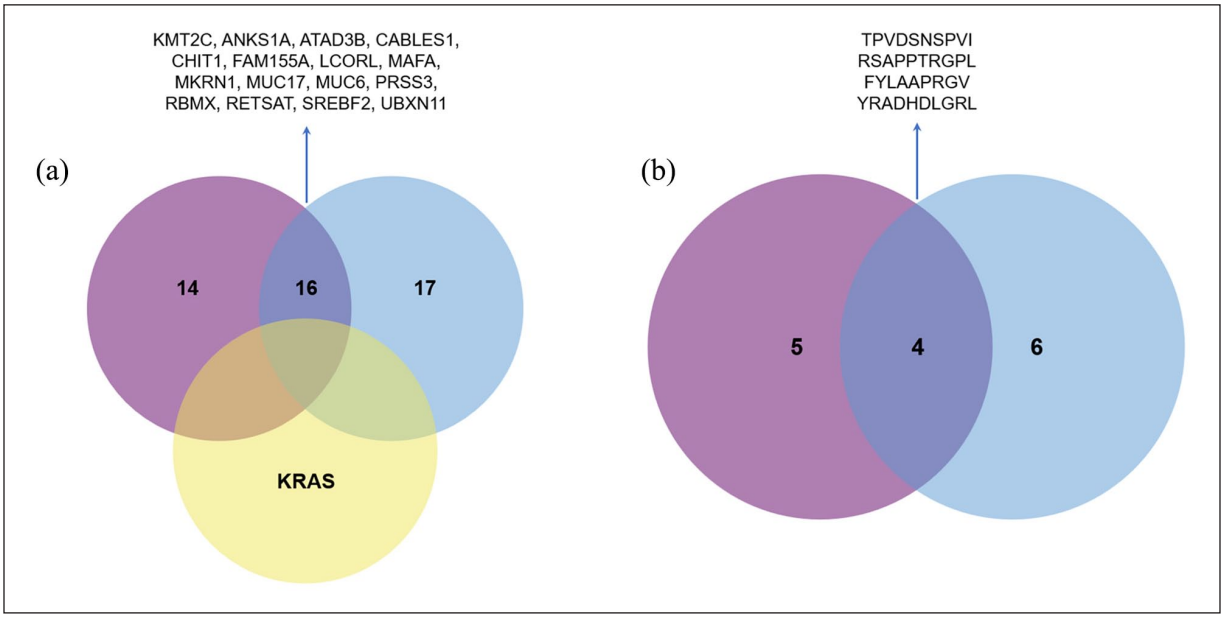

Figure 3. Results of lung cancer testing of nine genes and whole-exome sequencing detection of prostate cancer and intrahepatic cholangiocarcinoma. (a) The gene mutations in lung cancer, intrahepatic cholangiocarcinoma, and prostate cancer are subjected to an intersection assessment; (b). The predicted neoantigen peptides are subjected to an intersection assessment.

(Endostat) 30-mg i.v. drip qd d1-7 anti-tumor angiogenesis therapy for one cycle, while applying bicalu Amine 50-mg po qd antiandrogenic treatment. The patient's general condition gradually deteriorated. Re-examination of CT after 2 months revealed the progress of lung and liver lesions and brain metastases (Figure 4). Overall Survival (OS) was 5 months.

Discussion

Thyroid cancer and lung cancer are two of the most common malignancies worldwide. The incidence rate of thyroid cancer is 3.2 cases per 100,000 individuals globally, and the mortality rate is 0.5 cases per 100,000 individuals.[6] Intrahepatic cholangiocarcinoma is a rare histopathological type of primary liver cancer, which accounts for only 5%–10% of liver cancer.[7] The occurrence of multiple primary malignancies in a single patient has been relatively rare, despite the increasing overall incidence of malignancies. Subsequent reports also found cases of intrahepatic cholangiocarcinoma with bone metastases and thyroid cancer,[8] or combined with gastric cancer.[9] At present, there has been no case report on the simultaneous MPC of lung cancer, intrahepatic cholangiocarcinoma, and prostate cancer. There have also been no reports on the use of WES to study pathogenesis from the genetic level on this kind of MPC.

By analyzing the WES of this patient and consulting relevant data, we found that these same mutants are involved in multiple links of tumor formation in the human body, including cell proliferation,[10–12] cell cycle regulation,[13] genetic stability,[14] metabolism,[15,16] cell invasion,[3,17,18,19] angiogenesis,[20,21] and cell apoptosis.[22] This suggests that the patient had mutations in each promotive and inhibitive link of tumor formation, rendering him more likely to develop tumors. There are several identical tumor neoantigens in intrahepatic cholangiocarcinoma and prostate cancer tumor tissues, and the repetition rate is close to 50%. This further shows that pathway abnormalities were involved in the formation of these two tumors.[23] Only nine genes in lung cancer tissues were sequenced, and mutation was observed only in *KRAS*.

Previously, mutational load was suggested to be a limiting factor for responsiveness to checkpoint blocker therapy; however, a recent study showed that even tumors with low mutational load are responding. Thus, the identification of neoantigens peptides that are immunogenic might help to stratify the patients. Moreover, predicting immunogenicity of neoantigens will also dramatically improve cancer vaccination. In this case, there had no somatic variation of clinical significance, combine with the result of TMB-L and microsatellite stability (MSS) displayed that the patient was unable to NGS-directed targeted therapy or immunotherapy for prostate cancer and intrahepatic cholangiocarcinoma focus. We hope to find more directions of treatment through neonatal antigen prediction, and also provide treatment guidance for similar patients in the future.

The patient survived only a few months, so we cannot provide information on patient follow-up in the Case Report section, and the treatment had poor results. This can be attributed to the late stage of the patient's condition, large tumor burden, poor physical status, and inability to tolerate sufficient multidrug combination therapy, as well as to the patient's straitened economic condition and personal factors, and the treatment team did not attempt other anti-tumor drugs. Furthermore,

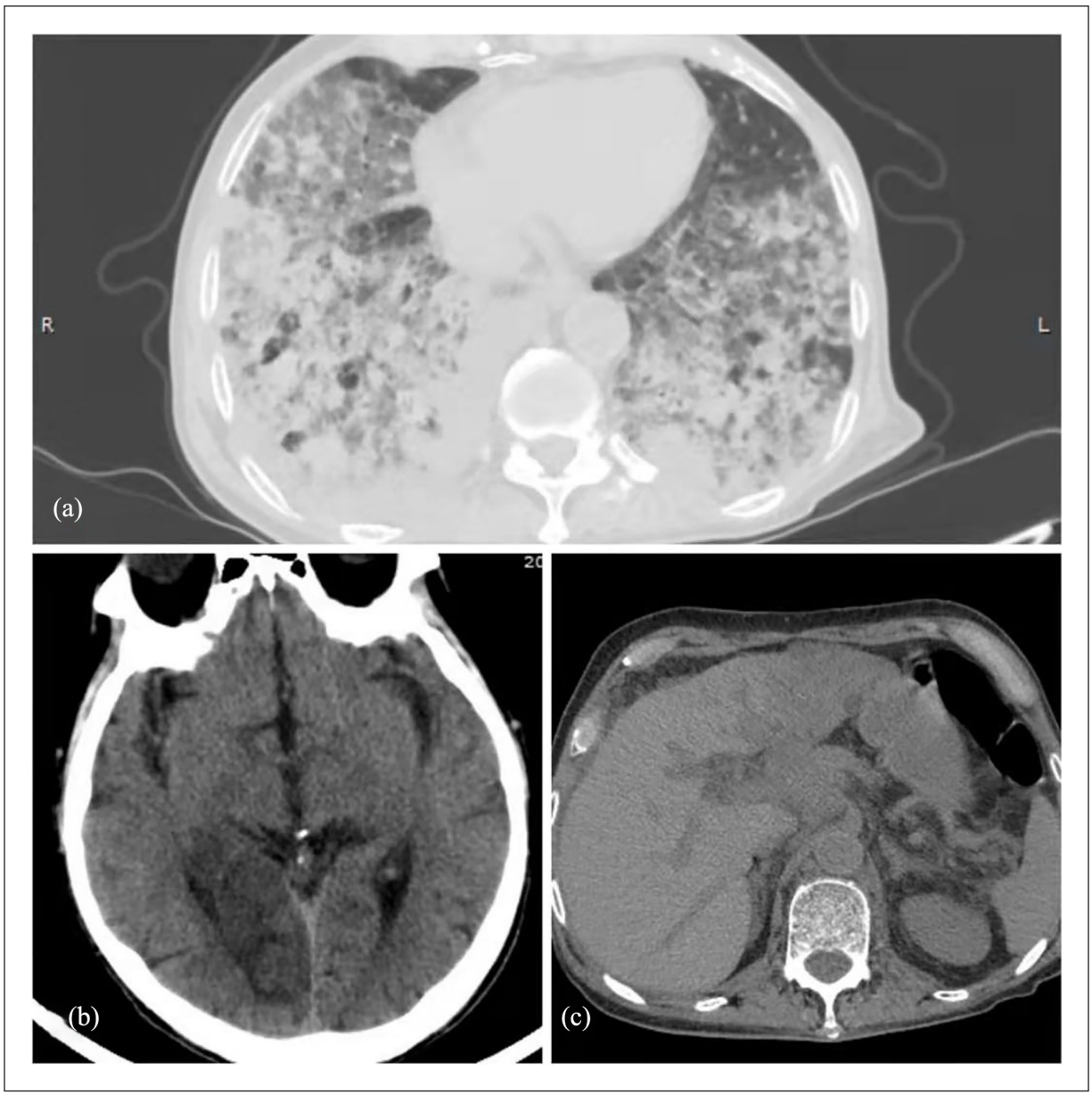

Figure 4. Computed tomography review results. (a) Progression of lung lesions; (b) progression of brain metastases; (c) progression of liver lesions.

there is no recommended treatment plan for complete coverage of three primary tumors in independent body systems.

Due to the small amount of sample tissue and the large number of mutated genes, it is impossible to determine whether there are key gene mutations. Follow-up studies should be conducted with a larger sample size or greater coverage of genetic testing.

Conclusions

In conclusion, the formation of MPCs is related to the loss of one or more lines of the body's anti-cancer defense system. This loss of control may be congenital or acquired. There is no pattern in the location of the disease. Except the head and neck cancer has regions, in other MPCs, the occurrence sites is aways related to the living environment of patients which may mainly be characterized by increased susceptibility to tumors after exposure to carcinogens. Whether there are key gene mutations in MPC needs to be validated by large-sample data analysis. Due to the defects in or breakdown of the body's anti-cancer defense system, the explanation for the occurrence of multiple primary and multiple system tumors may be an expanded version of field cancerization. More extensive and in-depth genetic testing may provide a basis for finding the cause of MPCs and developing suitable treatment.

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Author contributions

T.Z., X.L, H.S. participated directly in the care and diagnosis of the patient as members of the multidisciplinary oncology team, whereas H.Z. performed pathology and genetic studies. All authors performed the literature review and drafted, reviewed, and approved the final version of the case report.

Availability of data and materials

All data generated or analyzed in this study are included in the published article. The datasets generated and/or analyzed during the current study are available in the NCBI repository, and the reference sequences used are available in the following link: https://www.ncbi.nlm.nih.gov/nuccore/NC_000002.11; https://www.ncbi.nlm.nih.gov/nuccore/NC_000007.13; https://www.ncbi.nlm.nih.gov/nuccore/NC_000010.10, et al.

Declaration of conflicting interests

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Ethics approval and consent to participate

Written informed consent was obtained from the patient's families.

Consent for publication

Written informed consent was obtained from the patient's families for publication of this case report and all materials. These materials include clinical details, characteristic phenotypic information, genetic testing results and other related data used in this report. A copy of the written consent is available for review by the Editor of this journal.

Supplemental material

Supplemental material for this article is available online.

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