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CASE REPORT

Should we Continue to Monitor or Choose to Ignore the Mild Increase in CA19-9 after Surgery

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SUMMARY

Background: **Different detection platforms can lead to significant differences in the results of CA19-9. Here, a case of a 38-year-old male colon cancer patient who underwent CA19-9 testing on two platforms after surgery.**
Methods: **We first inspect the instrument to confirm its normal operation and good indoor quality control. Then, we conduct dilution experiments to eliminate interference from heterophilic antibodies, compare and analyze inherent differences with other platforms, and regularly follow up to dynamically monitor the patient's condition.**
Results: **During follow-up, the patient's CA19-9 levels rose consistently on both platforms, leading to tumor recurrence two years later, missing optimal treatment.**
Conclusions: **Dynamic monitoring of tumor markers should be based on a stable platform and combined with imaging examinations. For abnormal elevated results, humanistic care is needed to address the patient's fear and doubts about the test results.**
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KEYWORDS

CA19-9, postoperative, recurrence, standardization

CASE PRESENTATION

The complainant is a 38-year-old male patient who reported discovering rectal bleeding accompanied by incomplete stool in March 2018, which lasted for three months without improvement. Then in June, he underwent radical colon cancer surgery at a local hospital in Suzhou, and the postoperative pathology showed moderately differentiated adenocarcinoma of the transverse colon (ulcerative mass, size 5.5 x 4.5 x 1 cm), with cancer tissue infiltrating the entire intestinal wall and visible invasion of nerves and adjacent gastric tissue outside the mesentery. On June 19, July 11, August 2, and August 30, 2019, a total of 4 chemotherapy sessions were performed. In the same year, the outpatient examination in our hospital on December 1 showed that the serum CA19-9 concentration had increased (104.37 U/mL); then, on December 25, the outpatient clinic reexamined tumor markers, and the serum CA19-9 concentration continued to increase (189.59 U/mL); on Jan-

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uary 8, 2020, serum CA19-9 was re-examined (235.24 U/mL). Since the patient's CA19-9 continued to increase after the above chemotherapy course, the physicians in our hospital suspected tumor recurrence. He was admitted to our hospital for chemotherapy with FOLFOX regimen.

The patient subsequently underwent an outpatient examination for CA19-9 (15.98 U/mL) at another hospital in Nanjing on June 10, 2020, and stopped chemotherapy due to normal results. In the face of two different results, the patient is more willing to believe in the normal results, and the condition is developing in a good direction. According to his self-perception and imaging examination results, he complains that our results are wrong, leading to excessive treatment and psychological damage, so he disagrees with us (Figure 1A).

DISCUSSION

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States. There will be 1,958,310 new cancer cases and 609,820 cancer deaths occurring in 2023 [1]. Therefore, the more effective method is to detect cancer at the early stage, which can make the treatment more effective, with fewer side effects, and improved long-term survival. However, as detection methods become increasingly sensitive, it can be difficult to distinguish inconsequential changes from lesions that will lead to life-threatening cancer [2]. One of the most important methods is to detect tumor markers, including protein markers and nucleic acid markers. Alpha-fetoprotein was first proposed as a tumor marker of hepatocellular carcinoma in the 1960s, and protein markers have been widely used in clinic [3]. Nevertheless, the global standardization of tumor marker detection results cannot be achieved due to the lack of ideal quantitative traceability system, neither reference measurement procedures nor reference materials for calibration, and most of them apply the manufacturer's internal standards for metrology traceability [4]. Carbohydrate antigen 19-9 (CA19-9), a typical representative, which is the best validated biomarker, predictor, and promoter in pancreatic cancer [5]. In addition, CA19-9 was found to be elevated in colorectal, lung, liver and ovarian malignant tumors, as well as some benign diseases, including hepatobiliary diseases, pneumonia, pleural effusion, etc. [6]. Abbott's data shows 94.4% of healthy individuals have CA19-9 $\leq$ 37 U/mL. Due to the inconsistency of test results in different laboratories and improper clinical use, an abnormal CA19-9 result came to us.

We reviewed and analyzed the alarm information, calibration and quality control of the analyzer during the detection period, and the influencing factors of blood collection, and no abnormalities were found. With the consent of the patient, the result of blood re-collection on June 11 was 163.45 U/mL, which was still quite different from other hospitals. It has been reported in the literature [7] that some individuals have heterophilic antibodies that can react with labeled antibodies in reagents and interfere with *in vitro* detection, which can be weakened or counteracted by dilution methods. For this reason, we diluted the specimens on June 11 and tested them in different proportions, and found that the results did not change significantly (Table 1).

The patient's situation has aroused our special attention. After investigation, we found that the two laboratories used different analysis platforms, namely our Abbott and the other Roche. In fact, different manufacturers of tumor marker detection reagents target different antigenic epitopes [8]. Although the *in vitro* tumor marker detection has a history of more than 30 years, there is still no complete traceability of most tumor markers, including CA19-9. The lack of traceable international standards also directly leads to differences in the results of different testing platforms. In order to find out the reason, it is recommended to use different detection platforms simultaneously for follow-up and comparison based on patient trust. We collected 91 serum samples with the concentration covering the linear range, and the split samples were tested on two platforms for correlation analysis (Figure 1B). We used the SPSS paired samples *t*-test to analyze the results and found that, although the two sets of data were correlated, $R = 0.696$ ($p < 0.001$), there were significant differences between the two sets of data, $t = 4.84$ ($p < 0.001$). The two sets of data are incomparable. But what attracts our attention is that the detection results of both platforms show an upward trend in the subsequent detection process, and Abbott's rise is higher than Roche's (Figure 1C).

As mentioned above, the patient stopped chemotherapy due to the normal CA19-9 reexamination on June 10, 2020, and was regularly injected with thymosin in the hospital. The CA19-9 gradually increased to 179 U/L in monthly reexamination when reexamined one month later. Therefore, the patient underwent PET-CT examination in the Third hospital in Nanjing on November 10, 2020. The results showed that the transverse colon cancer changed after operation, and no abnormal soft tissue shadow and increased FDG metabolism shadow were found at the anastomosis. There is an enlarged lymph node below the pancreas, with unclear boundary with the pancreas and increased FDG metabolism. Consider the possibility of lymph node metastasis or involvement of the pancreas. Then chemotherapy was performed in the general surgery department of our hospital in November and December 2020 and January, February, and March 2021. On April 12, the 3.0T whole abdominal MRI plain scan and enhanced examination were reviewed in our hospital, which suggested that the anterior lower part of the pancreas was occupied, and the possibility of lymph node metastasis was considered.

CA19-9 is synthesized in the normal pancreatic parenchyma and biliary tract and can also be produced by epithelial cells of the gastric, colon, and uterine mucosa, as well as by the salivary glands. In addition to malignancy, CA19-9 is known to be increased in benign pan-

Table 1. Comparison of the detection results of CA19-9 (U/mL) diluted in different proportions.

Dilution ratio	Undiluted	1:1	1:3	1:7	1:15	1:31
Test result [a]	163.45	165.10	159.68	168.85	158.51	167.76
Bias [b]	/	1.01%	-2.31%	3.30%	-3.02%	2.64%

[a] The diluted result has been multiplied by the corresponding dilution factor. [b] The bias is less than or equal to 15% (standard source: ISO 18113-1:2022).

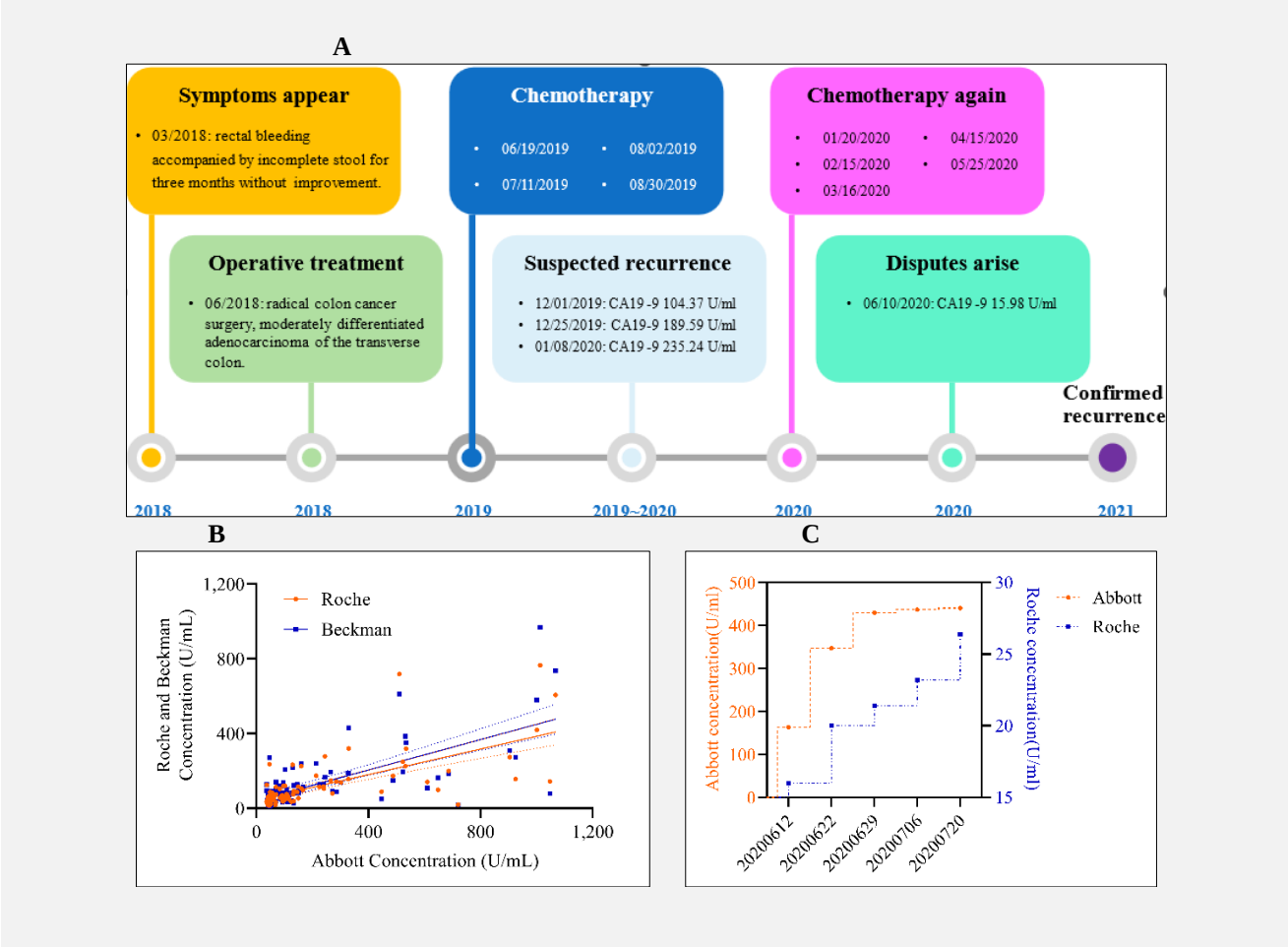

Figure 1. Summary of the progress of the patient's condition and analysis of the causes of abnormal results.

A. Timeline of patient from initial disease onset to diagnosis of recurrence. B. Correlation analysis between Abbott, Roche, and Beckman platform. C. The changes of CA19-9 were dynamically observed by Abbott and Roche platform simultaneously.

creatobiliary, hepatic, and pulmonary diseases as well as thyroiditis, diabetes, and autoimmune diseases. Therefore, caution should be exercised in interpreting the significance of CA19-9 level [9].

This case is a male colon cancer patient who attracted our attention due to the large difference in CA19-9 detection in different hospitals. First, *in vitro* detection errors caused by heterophilic antibodies in individuals can be eliminated by dilution experiments. However, little difference was observed in dilution results in this case, suggesting other causes. Studies show that most tumor markers lack international standards, no reference measurement methods and traceability chains. There are differences in reagents, quality controls, and calibrators of

different detection platforms and lack of reference standards. At the same time, the epitopes of Abbott and Roche detection platforms for CA19-9 are also different. To this end, we collected 91 specimens from the two platforms for comparative analysis and found that although the data of the two platforms were correlated, the data differences were obvious and the differences were statistically significant ($p < 0.05$). Hence, CA19-9 values vary by brand, and no single instrument's results are definitive. Correction or comparison via parameters/percentages is not feasible.

At the same time, in the process of follow-up, we found that the patient's detection results on both platforms showed an increasing trend, confirming the recurrence and metastasis of the tumor in subsequent imaging examinations and surgery. The unusual CA19-9 situation of this case suggests that we should use the same detection platform to dynamically observe the changes of CA19-9 level and follow up, adopt appropriate monitoring strategies, and carefully adopt diagnosis and treatment methods. At the same time, due to the patient's fear of tumor and tumor treatment, negative psychological self-defense, escapism, and preconceived assumptions that the high result is wrong, patients often require medical staff to give more humanistic care as part of the treatment of malignant diseases such as tumors. At the same time, each report should explain the method used for analysis. The test results of different platforms cannot be replaced with each other and communication should be strengthened between laboratory, clinical, and patient to minimize the burden on patients.

Declaration of Interest:

None.

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