Case Study 1

Tumor Markers in Type 2 Diabetes: Alarming Findings

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CASE REPORT

Case 1

A 66-year-old male with type 2 diabetes mellitus (T2DM) of 18-year duration. Enrolled at a center in 2006. On regular telemedicine follow-up and physical visits 2–3 times a year. No other co-morbidities. Active and energetic. Exercises regularly for 30 minutes daily. Not a smoker. Not an alcoholic.

During a routine follow-up in 2019, following were the patient's physical and laboratory parameters:

- Body mass index (BMI) – 28.6 kg/m^2
- Blood pressure (BP) – 126/84 mmHg
- Glycated hemoglobin (HbA1c) – 6.5%
- Creatinine – 0.8 mg/dL
- Low-density lipoprotein (LDL) – 65 mg/dL
- Serum glutamic-pyruvic transaminase (SGPT) – 32 IU/L
- The following tumor markers were also done:
    - Alpha-fetoprotein (AFP) – 1.74 ng/mL (normal range: 0–7 ng/mL)
    - Prostate-specific antigen (PSA) – 0.928 ng/mL (normal range: 0–4 ng/mL)
    - Cancer antigen 19-9 (CA 19-9) – >1000 U/L (reference value <37 U/L).

Patient was totally asymptomatic despite the very high CA 19-9. Patient and family members were informed about the suspicious result. Initially they were not convinced about proceeding for further investigations, as the patient was free of symptoms. The test was repeated with same sample as well as with a fresh sample taken the next day. All yielded the same abnormally high result.

The possibility of false positive results and the significance of detecting a malignancy if any at an early stage was discussed tactfully. Patient was referred to specialty center where CT scan and PET scan were taken within the next 48 hours. The investigation revealed carcinoma confined to the tail of pancreas, a suspicious node with no evidence of metastasis elsewhere. Patient was referred to an advanced care center for cancer treatment. Radiologists and the oncology team were of the opinion that it is a very unusual case where the rather difficult detection of carcinoma pancreas before metastasis was made with the help of a laboratory test.

The tumor was surgically removed after a course of neo-adjuvant chemotherapy and according to the oncology team, they are expecting a complete cure. Patient is doing very well and continues to be physically and intellectually active.

Case 2

A 54-year-old male with T2DM since 2015, slightly obese. No other comorbidities. The patient was on regular telemedicine follow-up and physical visits. Following were the observations during a routine follow-up:

- BMI – 33.3 kg/m^2
- HbA1c – 6.1%
- Creatinine – 1 mg/dL
- LDL – 54 mg/dL
- SGPT – 31 U/mL
- Spot – 22 mg/L
- CA 19-9 – 77.54 U/L

The patient was referred to a gastroenterologist where investigations such as MRI abdomen were conducted. All results turned out to be negative. Repeat CA 19-9 after 15 days showed a slight increase. Patient was not satisfied with a negative result in the evaluation of cancer and was not convinced with the discussion on false positive results with tumors markers. The patient went to a general physician who noticed that chest X-ray was not repeated for the last 4 years.

The patient took a chest X-ray and got back to us. The X-ray showed a suspicious shadow which was later diagnosed to be carcinoma lung. Further evaluation showed a primary malignancy arising from the middle lobe of the lung. The patient was initiated on chemotherapy followed by sleeve lobectomy. The patient got back to us 5 months later only to make sure that CA 19-9 has dropped and is within normal limits (from 77.54 U/L to 37.84 U/L).

The patient kept on repeating CA 19-9 once in every 4 months despite the authors insisting that it is not necessary. In April 2019 he found that CA 19-9 was again showing an upward trend (48.3 U/L). Preliminary evaluation was carried out at the center where he was getting treated for malignancy. Most of these tests were carried out due to patient insisting on it. A couple of weeks later, a recurrence of the previous lung malignancy was confirmed. He is currently on chemotherapy.

Case 3

A 54-year-old male with T2DM of 33 years duration. Enrolled at a center in 2004. On regular telemedicine follow-up and physical visits. No smoking or alcoholic history. No other comorbidities. During routine follow-up visit in April 2011, following were his physical and laboratory parameters:

- BMI – 22.0 kg/m^2
- BP – 112/57 mmHg
- HbA1c – 6.3%
- Creatinine: 0.8 ng/mL
- LDL: 79 mg/dL
- SGPT: 18 IU/L
- PSA – >100 ng/mL

The patient was referred to a urologist and diagnosis of prostate cancer was confirmed. The patient was referred to cancer center where individualized tumor response testing (ITRT) and intensive treatment with radiotherapy was carried out. The patient is on regular follow-up. Eight years after diagnosis, patient remains asymptomatic and very active.

Case 4

A 69-year-old male with T2DM of 15 years duration. No other comorbidities. On regular telemedicine follow-up and physical visits 2–3 times a year. Not a smoker. Not an alcoholic.

His physical and laboratory parameters during a routine visit were as follows:

- BMI – 23.1 kg/m^2
- BP – 135/57 mmHg
- HbA1c – 6.4%
- Creatinine – 1.0 mg/dL
- Urea – 20 mg/dL
- LDL – 69 mg/dL
- SGPT – 37 IU/L

The possibilities of doing some tumor markers were also discussed and the patient agreed. Couple of markers were done and among them CA 19-9 was marginally elevated (47.6 U/L).

Since this has been observed in many patients with chronic liver disease where serial values of tumor markers will remain same or drop over a period, the authors discussed the result with the patient and advised to repeat it after one month. On repeat testing, the value was found to have increased (73.34 U/L).

The patient was referred to gastroenterology specialty center where he was further evaluated. MRI and other investigations did not reveal any significant findings. After 3 months, CA 19.9 was reassessed, and the value was found to have increased further (110.1 U/L). Investigations revealed a suspicious growth in one of the segments of the liver. Though doctors discussed urgent resection of the segment of liver, the patient deferred from discussing this with his family members despite repeated requests from the treating team.

The patient continued clinic visits and repeated the tumor markers quite frequently (once in 2 months). The values were consistently rising (122.5 U/L in 2016 and 163.4 U/L in 2017) but the patient though affordable, quite friendly and very active, was unwilling for further treatment at specialty center. In late 2017, the family informed us of the patient being hospitalized with advanced stages of malignancy and expired 2 weeks thereafter.

In this case, though the diagnosis came quite early, the patient was not convinced about the result in the beginning but later when he came to terms with the diagnosis, he was unwilling to opt for treatment due to fear of interventions/treatment.

DISCUSSION

It is well known that certain malignancies are two-fold higher in T2DM. However, screening for cancers is not recommended in any clinical guidelines. Here, the authors are discussing 4 different cases of T2DM where tumor markers performed during routine clinic visits revealed presence of early malignancy and have turned out to be life-saving.

The authors have discussed four different cases here. The first case is that of early detection of cancer at the tail of pancreas. Tumors of the body and tail of the pancreas constitute one-third of the pancreatic neoplasms and have been associated with a poor prognosis due to the late presentation. They often attain a large size with local invasion before they produce any clinical symptoms. According to the American Cancer Society, for all stages of pancreatic cancer combined, the 1-year relative survival rate is 20%, and the 5-year rate is 7%. Thus, the prognosis of this type of cancer is, generally, poor. In this case, early detection was possible only because of a tumor marker being done before metastasis and before the occurrence of symptoms such as pain.

In the second case where a diagnosis of carcinoma lung was made, it was interesting to note that it was CA 19-9 (a marker specific for pancreatic, gallbladder, bile duct, and gastric cancer and not for lung) which was elevated. This raises the question as to whether these markers really need to be specific when it comes to screening for cancer. The case also becomes an eye opener for the physician to evaluate further and beyond the specified organs, if a tumor marker is either elevated or continues to show an increasing trend.

The third case is that of a patient in whom prostate cancer was diagnosed after screening using the PSA test. It was in 1994, that the FDA approved the use of PSA test in conjunction with a digital rectal exam (DRE) to test asymptomatic men for prostate cancer. In the case of this patient, his earlier PSA levels had remained normal and the onset was sudden. This elderly gentleman continues to remain active, 8 years after the diagnosis was made.

The fourth case is different from the rest of the cases since it is a case of failure. When the authors could save the lives of all the three patients with T2DM mentioned in the first 3 cases, the fourth patient though made aware of the significance of an elevated tumor

marker, chose not to get treated. The patient who was initially not convinced of the result, later kept on repeating the marker which was increasing in number proportionate to the increase in the size of tumor.

Incidence of Malignancies in Diabetes

Type 2 diabetes mellitus is associated with increased risks for several cancers, including colon, postmenopausal breast, pancreatic, liver, endometrial, bladder cancers and non-Hodgkin's lymphoma. The relative risk imparted by diabetes are two-fold or higher for cancers of the liver, pancreas, and endometrium and about 1.2–1.5 fold for cancers of the colon and rectum, breast, and bladder. Meta-analysis of 20 studies found a 50% increased risk of pancreatic cancer in patients with T2DM diabetes of duration more than five years.

Diabetes and cancer share common risk factors such as aging, obesity, diet, and physical inactivity and possible mechanisms for a direct link between diabetes and cancer include hyperinsulinemia, hyperglycemia, and inflammation.

Tumor Markers and its Routine Use

The two main types of tumor markers in cancer care are circulating tumor markers and tumor tissue markers.

Circulating tumor markers are used to:

- Estimate prognosis in cancers
- Detect cancer that remains after treatment or that has returned after treatment
- Assess the response to treatment
- Monitor whether a cancer has become resistant to treatment.

Tumor tissue markers are found in a sample of the tumor that is removed during a biopsy.

Thus, tumor markers are routinely used only in oncology for evaluating the prognosis in those getting treated for respective malignancies and rarely for diagnosis. Tumor markers are not recommended as a screening test in asymptomatic subjects with T2DM. This is because non-cancerous conditions can sometimes cause the levels of certain tumor markers to increase. In addition, not everyone with a cancer will have a higher level of a tumor marker associated with that cancer. Therefore, measurements of circulating tumor markers are usually combined with the results of other tests, such as biopsies or imaging, to diagnose cancer.

Some of the tumor markers that are in common use, mainly to determine treatment or to help make a diagnosis of cancer are as follows:

Cancer Antigen 19-9

- Cancer types: Pancreatic, gallbladder, bile duct and gastric cancers
- Use: To assess whether treatment is working.

Alpha-fetoprotein

- Cancer types: Liver cancer and germ cell tumors
- Use: To help diagnose liver cancer and follow response to treatment; to assess stage, prognosis and response to treatment of germ cell tumors.

Prostate-specific Antigen

- Cancer type: Prostate cancer
- Use: To help in diagnosis, to assess response to treatment and to look for recurrence.

Carcinoembryonic Antigen (CEA)

- Cancer types: Colorectal cancer and some other cancers
- Use: To keep track of how well cancer treatments are working and check if cancer has come back or spread.

Cancer Antigen 125

- Cancer type: Ovarian cancer
- Use: To help in diagnosis, assessment of response to treatment and evaluation of recurrence.

Calcitonin

- Cancer type: Medullary thyroid cancer
- Use: To aid in diagnosis, check whether treatment is working and assess recurrence.

Limitations

The three most important characteristics of an ideal tumor marker are:

- It should be highly specific to a given tumor type
- It should provide a lead-time over clinical diagnosis and
- It should be highly sensitive to avoid false positive results.

Since tumor markers are used to assess response to treatment and prognosis, it has been hoped that they might also be useful in detecting cancer early, before there are any symptoms. However, there are no tumor markers identified as sufficiently sensitive or specific to screen for cancer. Possible increases or false positives in the case of non-cancerous diseases are also indispensable. Due to this reason, when the tumor marker result shows a borderline high, the physician is faced with the dilemma of whether or not to initiate the discussion of a possible malignancy with the patient. In the case of very high levels of a tumor marker, the discussion of a possible malignancy and the urgent referral to the concerned specialist must be cautiously made and the urgency properly communicated.

CASE CLINICAL PEARLS

- In diabetes, there is higher prevalence of coronary artery disease, stroke and chronic kidney disease for which established and recommended screening tests are available. However, tumor markers are currently not recommended in the routine care of diabetes and are seldom recommended as an executive test. However, given the two-fold increased risk of occurrence of malignancies in diabetes, it is justified to perform tumor markers for screening in asymptomatic adults with diabetes
- We also need to amass more evidence to prove tumor markers as a cost-effective investigation in diabetes
- The crucial point that must be considered is that if tumor makers can detect early-stage disease where the chance of a cure is high, performing tumor makers in T2DM might have a definitive role, given the higher prevalence of certain cancers in adults with diabetes
- If an investigation, though expensive and not recommended for screening, turns out to be life-saving for patients, it is fully justified for recommending it as a screening test for asymptomatic high-risk patients and diabetes tops the list.

SUGGESTED READINGS

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