



Colchicine may cause elevated serum levels of CA72-4: Case series

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Abstract

Colchicine is used in the treatment of Behçet's disease, familial Mediterranean fever, gout arthritis, pericarditis, some inflammatory and fibrotic diseases by extracting it as an alkaloid from the plant named Autumn Crocus, which is from the lily family. CA 72-4, which has a glycoprotein structure, is especially useful in the diagnosis and follow-up of gastrointestinal adenocarcinomas as well as its serum level can be increased in pancreatic, ovarian, endometrial, and breast cancers. No drugs that cause CA 72-4 rise have been reported to date. In this article, four patients who were referred to our clinic because of CA 72-4 serum elevation and who used colchicine for various reasons are presented.



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Introduction

Colchicine is a drug used in the treatment of Behçet's disease, familial Mediterranean fever (FMF), gout, pericarditis, some inflammatory and fibrotic diseases by extracting it as an alkaloid from the plant named Autumn Crocus, which is from the lily family [1]. Although it has been used for thousands of years by the world, it was discovered in 1950. It acts by targeting the microtubules that constitute the majority of the cellular skeleton between the cell membrane and the nucleus, and are responsible for mitosis and intracellular organelle and vesicle traffic [2]. Colchicine alters its confirmation by binding to tubulin heterodimers, allowing the tubulin dimer-colchicine complex to attach to the growing end of a microtubule, but inhibiting its further growth, thereby causing microtubule destabilization [3].

Serum tumor markers are used in the diagnosis, prediction of survival, and post-operative monitoring of malignancies [4,5]. Carcinoembryonic antigen (CEA), Carbohydrate Antigen (CA) 19-9, and Carbohydrate Antigen (CA) 72-4 are frequently used clinical markers of gastrointestinal

carcinomas. CA 72-4, which has a glycoprotein structure, is especially useful in the diagnosis and follow-up of gastrointestinal adenocarcinomas as well as its serum level can be increased in pancreatic, ovarian, endometrial, and breast cancers [6-8]. It has also been shown to be elevated in non-neoplastic conditions such as type 2 diabetes mellitus, pancreaticobiliary diseases and liver fibrosis [9,10]. Finally, the relationship between some fungi and ganoderma lucidum (Reishi mushroom) spore powder and the height of CA 72-4 has been reported [11,12]. No drugs causing an increase in CA 72-4 have been reported so far.

In this article, four patients who were referred to our clinic due to elevated CA 72-4 serum level and who used colchicine for various reasons are shown.

Case Report

Case 1

A 31-year-old male patient was admitted to the Rheumatology outpatient clinic 3 months ago due to edema, redness, pain and temperature increase on the right foot 1st metatarsal medial face and was diagnosed with gout arthritis. The patient was started on colchicine 3 mg/day and ibuprofen 400 mg bid. The patient's complaints ended, one month later, when he went to the checkup, in the

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blood tests performed at the patient's request, complete blood count (CBC), kidney and renal function tests were normal, uric acid was 8.5 mg/dl (0-5 mg/dl), CA 72-4 was high (77.5 U/ml; reference range: 0-6.5 U/ml) and CEA, CA125, CA19-9, PSA were normal. The patient was referred to the Gastroenterology outpatient clinic. Since no pathology finding was detected in the physical examination of the patient and there was no alarm symptoms, screening program was not implemented and the colchicine treatment was discontinued and allopurinol was started instead. In this period, the patient's active arthritis findings and acute phase reactants were observed at a normal level. The CA72-4 level was 2.6 U/ml (within the normal range) following the fourth week of discontinuation of colchicine. The patient was informed about his condition and colchicine treatment was started again at the same dose. Two weeks after resuming treatment with colchicine, it was found that CA 72-4, which was tested for control, was 45.2 U/ml.

Case 2

A 40-year-old female patient, who was followed for FMF for 4 years, was consulted to the Gastroenterology department due to the increased frequency of abdominal pain. Abdominal pain accompanied by constipation in the left lower quadrant and a decrease in pain after defecation. In the blood tests performed due to routine check-up in the rheumatology outpatient clinic, CA 72-4 level was found to be high (18.4 U/ml). The physical examination revealed no pathology. CBC, renal function tests, liver function tests, CRP and ESR values were within normal range. Since there was a family history of gastrointestinal cancer (her father's case of colon cancer), malignancy screening was performed and normal ileocolonoscopy findings were found in colonoscopy, and antral gastritis was found in esophagogastroduodenoscopy (EGD). Abdominal computed tomography (CT) and breast ultrasound were normal. Since the patient was not active in terms of FMF, colchicine was discontinued and the CA 72-4 level measured 4 weeks later was found to be 4.06 U/ml.

Case 3

A 55-year-old female patient, who was followed for rheumatoid arthritis, was referred to gastroenterology outpatient clinic after a CA 72-4 elevation (47.6 U/ml) was detected in routine control. Other tumor markers (CEA, CA 19-9, CA 125, AFP) were normal. The patient had no symptoms or signs of malignancy in the physical examination. The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for myoma uteri 10 years ago. One month ago, she was examined in the obstetrics clinic. In the breast USG and mammography examination, a cystic lesion of approximately 7 mm in size was detected in the left breast at 3 o'clock and follow-up was recommended. In laboratory tests, renal and liver function tests were observed to be normal. Although he did not have active arthritis, the patient had deformities in the bilateral hand and wrist joints. The patient was using colchicine 1.5 g/day, prednisolone 2.5 mg/day, hydroxychloroquine 400 mg/day and naproxen sodium 500 mg/day. In the colonoscopy performed on the patient, one

polyp with a size of 10 mm was removed from the transverse colon and its pathology was reported as tubular adenoma. No pathology was detected in the abdominal CT scan. No sign of malignancy was observed in the upper GI endoscopy. The colchicine used by the patient who did not have active arthritis was discontinued and the control CA 72-4 level at the 3rd week was 2.4 U/ml.

Case 4

An 82-year-old female patient, who had been followed for 30 years for the diagnosis of FMF, presented with abdominal distension. Physical examination revealed bilateral pretibial edema, hepatosplenomegaly and grade 3 ascites. In laboratory tests, hemoglobin: 10.4 g/dL (12-14 g/dL), platelet: 134000/mm³ (150.000-400.000/mm³), WBC: 8900/mm³ (4500-12000/mm³), albumin: 2.3 g/dL (3.5-5.2 g/dL), ALT: 21 U/L (0-35 U/L), AST: 97 U/L (0-35 U/L), ALP: 105 U/L (33-98 U/L), LDH: 832 U/L (0-259 U/L), total bilirubin: 1.65 mg/dL (0.3-1.2 mg/dL), direct bilirubin: 0.4 mg/dL (0-0.2 mg/dL), creatinine: 0.95 mg/dL (0.5-0.95 mg/dL), ESR: 69 mm/h (0-15 mm/h), CA 72-4: 125.8 U/mL (0-6.5 U/mL), CEA :8.4 ng/mL (0-5 ng/mL), CA 19-9: 1.2 U/mL (0-37 U/mL), AFP:7 ng/mL (0-40 ng/mL), CA 125: 499 U/mL (0-35 U/mL). In paracentesis sampling, serum acid-albumin gradient (SAAG) was measured as 1.5 and acid protein was 0.8 g/L. No malignant cells were detected in acid cytology and no bacterial proliferation in acid culture. In the USG, the hepatic contours were lobulated locally and a diffuse intraabdominal fluid was observed. Thrombosis was not found in the portal and splenic veins in Doppler USG. No mass was observed in abdominal CT. Pulmonary artery pressure was measured as 50 mmHg (8-20 mmHg), 3rd degree tricuspid regurgitation, ejection fraction: 40% (normal range:50%-75%) in the echocardiography. Liver cirrhosis due to heart failure was considered and metoprolol 50 mg/day and furosemide 40 mg/day were started. In the follow-ups, it was observed that the peripheral edema of the patient decreased and his complaints regressed. The colchicine used by the patient was discontinued and 3 weeks later the CA 72-4 value was found to be normal (4.5 U/ml).

Discussion

It was observed that the abnormally high CA 72-4 levels in our 4 cases presented above and who were using colchicine for various reasons, returned to normal after colchicine was discontinued (approximately 3-4 weeks). In one of our cases, it was found that the CA 72-4 level increased again 2 weeks after the colchicine was started again.

Although tumor markers are used for diagnosis, survival prediction and postoperative recurrence in malignant diseases, their use in the diagnosis of malignant diseases is very limited. Especially in the current guidelines, CA 72-4 has no place in the diagnosis of gastrointestinal malignant tumours. Unfortunately, this test is often used for the detection and diagnosis of gastrointestinal malignant tumours in outpatient clinics. High detection of 72-4 CA levels results in unnecessary investigations, increasing intensity and costs in the healthcare system. Tumor markers can also be elevated in non-neoplastic illnesses. It should be kept in mind that some fungi and *Ganoderma lucidum*

spore powders can increase the level of CA72-4 in serum. There are rare publications in the literature showing that the use of colchicine may cause increased CA72-4.

Zhao et al. indicated that they were investigated for malignancy when CA72-4 elevation was detected in a 51-year-old male patient during a routine check-up in 2018, but they could not reach a conclusion, and the CA 72-4 level returned to normal after the patient stopped colchicine for gout. Thereupon, they found all of the CA72-4 levels they sent from 9 patients using colchicine to be high [13]. Again, 143 gout patients (42: colchicine, 62: other treatments, 38: no treatment) and 40 healthy volunteers were compared and CA72-4 levels were compared to healthy volunteers in the colchicine group and to other treatment (Etoricoxib, Glucocorticoid, Allopurinol, Febuxostat, NSAID, Benzbromarone) was found to be significantly higher than those who received it. No significant difference was observed between the groups in the levels of AFP, CA19-9, CYFRA21-I, NSE, CEA and PSA. Serum CA72-4 levels were found to be above the normal level in all patients 4 days after they started using colchicine, while serum CA72-4 levels were within normal limits 4 weeks after stopping the drug [14]. On the other hand, Trape et al. examined 3 patients who received anti-inflammatory therapy for idiopathic pericardial effusion and stated that while CA72-4 levels were found above the normal value in 3 patients, they found other tumor markers within the normal range [15].

In the study of Bai et al., CA72-4 levels were found to be higher in gout patients with frequent attacks and colchicine use, compared to patients with a stable course, and it was suggested that elevated CA 72-4 levels were an important marker for predicting future attacks [16]. Finally, in a study comparing 36 FMF and 19 healthy volunteers, all of whom were using colchicine, it was found that high inflammation and high CA72-4 levels in those who had frequent attacks were correlated. No statistically significant difference was observed between the other tumor markers (CA 125, CA 19-9, CA 15-3, CA 72-4, CEA and AFP) compared to the control group.

It was emphasized that the high level of CA72-4 observed in patients with frequent attacks may be related to the current inflammation of the patient and the high-dose colchicine treatment given during the attack [17]. Unfortunately, these studies did not explain why colchicine increased the level of CA72-4, but it was reported that it had no effect on other tumor markers. In systemic diseases such as cancer and gout, glycan structures in the cell membrane often show dramatic changes and incomplete synthesis with the accumulation of precursor structures such as Sialosyl-a(2-6)-N-Acetylgalactosamine-a-Serine. As a result, this inflammation is thought to cause an increase in cancer biomarkers in glycoprotein structure such as CA72-4 [18,19].

Conclusion

Although tumor markers are frequently used in the monitoring of malignant diseases, their routine use in the detection of malignant tumors is not recommended. If it is found to be high in patients without any alarm symptoms, family history and clinical findings, it causes unnecessary

anxiety for the patient and also an unnecessary cost for the health system due to advanced examinations. Therefore, its use in routine clinical practice is not cost-effective. In patients who use colchicine and whose malignancy screening is negative, the clinician should explain to the patient that this situation is not associated with cancer and should comfort the patient.

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