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Two Cases of the Same Family with the Unusual Elevation of CA19-9 Levels



Dois Casos na Mesma Família com a Elevação Incomum de Níveis de CA19-9

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ABSTRACT

Introduction: Serum carbohydrate associated antigen (CA19-9) is widely used marker in clinical practice and shows small increases in a few benign diseases. Here we report two cases, a mother and her daughter with slightly elevated CA19-9 levels not accompanied by any clinical pathology.

Case Presentation: The mother with elevated CA19-9 level (89.90 U/mL; upper limit of normal range (ULNR) < 37 U/mL) was referred to our department for evaluation. Similar increase was determined in her daughter incidentally. Daughter's CA19-9 level was 123.92 U/mL. Extensive laboratory data, imaging procedures and clinical evaluations were within the normal ranges except elevated CA19-9 levels for both. Also, any pathology compatible with the elevated CA19-9 level couldn't be determined. In order to avoid laboratory errors and interferences, we measured the samples at four different immunoassay platforms twice.

Conclusion: Healthy people can be in excess of the ULNR. Therefore, clinicians need to be aware of these rare situations without missing the malignant disorders.

Keywords: CA-19-9 Antigen; Family; Tumor Markers, Biological.

RESUMO

Introdução: O antígeno carboidrato (CA19-9) presente no soro é um marcador amplamente utilizado na prática clínica e apresenta pequenos aumentos em algumas doenças benignas. Aqui relatamos dois casos saudáveis, uma mãe e a sua filha, com níveis CA19-9 um pouco elevados.

Casos Clínicos: A mãe, com um nível CA19-9 elevado (89,90 U/mL; limite superior do intervalo normal (ULNR) < 37 U/mL) foi encaminhada ao nosso departamento para avaliação. Um aumento semelhante foi incidentalmente determinado na sua filha. O nível de CA19-9 da filha era 123,92 U/mL. Os restantes parâmetros laboratoriais avaliados, estudos imagiológicos e avaliações clínicas revelaram-se dentro dos limites da normalidade. Não foi encontrada, qualquer patologia que justifique elevado nível de CA19-9. A fim de evitar erros de laboratório ou possíveis interferências, as amostras foram analisadas em quatro plataformas de imunoensaios diferentes, em duplicado.

Conclusão: As pessoas saudáveis podem ter níveis da CA19-9 superiores aos limites de referência. Portanto, os médicos precisam estar cientes dessas situações raras, sem falhar o diagnóstico de doenças malignas.

Palavras-chave: Antígeno CA-19-9; Família; Marcadores Biológicos de Tumor.

INTRODUCTION

The serum carbohydrate associated antigen (CA19-9, Sialyl Lewis-a) is a high molecular glycolipid which is a marker for both colorectal and pancreatic carcinoma, and is used in monitoring patients with these cancers in conjunction with imaging tests.¹ It shows small increases in a number of benign diseases, with highest levels in pancreatic adenocarcinoma, hepatocellular and cholangiocellular cancer, and also in gastric, colorectal, and occasionally other cancers (Table 1).²

Here we report two healthy cases, a 37-year-old mother

and a 16-year-old daughter, with slightly elevated CA19-9 levels. Additionally, to ensure the awareness of subjects relevant to this topic, we detected considerable differences between CA19-9 measurements with four different immunoassay methods.

CASE 1

A 37-year-old woman who was suffering from abdominal pain and presented mildly elevated CA19-9 level was referred to our department for evaluation. Her medical

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Table 1 - Causes of serum CA19-9 elevation (numbers in brackets correspond to the listed references)

Etiology	Serum CA19-9 levels	
	Marked elevation (> 1000 U/ml)	Mild elevation (< 1000 U/ml)
Malignancies²		
Biliary tract	+	
Pancreas	+	
Colon	+	
Stomach	+	
Female reproductive system		+
Cholestasis³	+	
Acute hepatitis⁴		+
Chronic liver disease⁵		
Non-alcoholic		+
Alcoholic		+
Cystic fibrosis⁶		+
Pancreatitis⁷		+
Diabetes mellitus⁸		+
Interstitial pulmonary disease		+
Collagen vascular diseases⁹		+
Endometriosis¹⁰		+
Case reports¹¹⁻¹³		
Hydronephrosis		+
Splenic cyst		+
Bronchogenic cyst		+
Hepatic steatosis		+
Colon diverticulitis		+
Hypothyroidism		+
Heavy tea consumption		+

history was unremarkable and there was no family history of any gastrointestinal malignancy. She was a nonsmoker and denied alcohol abuse or medication intake. Also, there were no abnormal physical examination findings.

Abdominal and pelvic ultrasonography (USG), computed tomography scan, upper endoscopy and colonoscopy were performed to evaluate intra abdominal abnormalities. Examination of the respiratory system and chest X-ray were normal. There was no abnormality or malignancy compatible with the elevated levels of CA19-9.

Laboratory data demonstrated that electrolytes, liver function tests (ALT, AST), urea, creatinine, CRP, ESR, amylase, lipase, whole blood count, fasting blood glucose, triglycerides, cholesterol, ferritin and thyroid function test (T3, T4, TSH) levels were within the normal range. Serum CA19-9 level was mildly elevated (89.90 U/mL) (Table 2). Other markers, including carcino embryonic antigen (CEA), alpha-fetoprotein (AFP), CA15-3 and CA125 were all within the normal range. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) value was 1.54.

In order to avoid analytical errors and interferences, we analyzed serum sample twice at four different immunoassay platforms: UniCel® DxI 800 (Beckman Coulter, USA), Roche Modular Analytics Elecsys E170 (Roche Diagnostics), Architect i2000SR, (Abbott Diagnostics, USA) and Advia

Centaur® XP (Siemens Healthcare Diagnostics Inc, USA). We also performed polyethylene glycol (PEG) precipitation to assess macro-complex interference and there was no difference after PEG precipitation.

All investigations for underlying malignancy were negative. After an incidental measurement, similar increase was determined in her daughter's serum CA19-9 level.

CASE 2

Then, 16-year-old daughter with the elevated CA19-9 level was evaluated (123.92 U/mL) (Table 2). Her medical history was unremarkable too. She had no complaints and symptoms. Additionally, the same laboratory tests were performed twice for the daughter. They were all in the normal ranges except CA19-9. HOMA-IR value was 0.79.

Moreover, similar investigations and evaluations confirmed the absence of any malignancy even in this patient. After a gynecological consultation, young girl was diagnosed with polycystic ovary syndrome (PCOS). Pelvic USG revealed bilateral polycystic ovaries.

Second measurements for both cases were performed after 2 months from the first analysis. The recheck levels were similar to the first ones. The results are given in Table 2.

Procedures were performed in accordance with the

Table 2 - The results of the samples of four different immunoassay platforms

Method				Architect i2000SR	Advia Centaur® XP	UniCel® Dxl 800	Elecsys E170
ULNR* (U/mL)				37	35	35	35
Serum CA19-9 Results (U/mL)	Mother	CA19-9 level on admission	First measurement	59.70	64.90	28.80	35.80
		89.9	Recheck measurements**	66.40	65.11	29.30	35.13
	Daughter	CA19-9 level on admission	First measurement	87.84	76.85	64.40	42.99
		123.92	Recheck measurements**	105.40	78.70	48.60	51.95

*ULNR: The upper limit of the normal range suggested by the manufacturers

**Recheck measurements: Second measurement after two months from the first analysis

Helsinki Declaration (revised in 2008). Both patients have signed an informed consent.

DISCUSSION

In these cases, the usual causes of CA19-9 elevation were ruled out. Both the mother and daughter did not refer any clinical situations related to conditions that urges CA19.9 increases, and frequently encountered types of malignancy that cause these elevations were excluded. All the laboratory data, upper and lower abdominal USG, colonoscopy and chest radiography did not reveal any pathology.

Although increased CA19-9 values have also been associated with hypothyroidism, our cases were euthyroid, and hypothyroidism was also excluded.¹³ Because the mother did not have polycystic ovaries, PCOS was not considered as the cause of CA19-9 elevation.

Furthermore, the concentration of a tumor marker in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods, types of antibodies and epitopes used, and reagent specificity. This was likely due to these two methods (the ADVIA Centaur and ARCHITECT i2000) use a single monoclonal antibody (1116-NS-19-9) for the 2-step sandwich immunoassay, whereas the other 2 (Elecsys E170, and UniCel Dxl 800) use one or more different antibodies. Different antibodies recognize different parts of the molecule, and heterogeneity or conformational alteration of the antigens may explain inter-method differences, partially. Accordingly, standardized reagents for tumor marker assays are needed to ensure the reliability of the results from different assays, and the standardization is also important for commutability among results from different assays in order to deal with increased patient mobility between hospitals. We considered that the exact underlying explanation for elevated CA19-9 was epitopal differences.

As manufacturers specified in their test manuals,

there are healthy people with excess of the upper limit of the normal range. The upper 97.5 % reference limit for all methods can differ from the manufacturers' upper limit of expected values for healthy subjects.¹⁴

Our cases highlight the importance of awareness of elevated tumor markers with no malignancies but also with benign diseases. False positives can lead to over-investigations and cause unnecessary anxiety to patients. Our hospital was the third hospital referred for this reason in the six-month period. Because it demands a time- and resource-consuming process, it is important that patients also should know her/his personal results to avoid being investigated for the same reason again and again.

CONCLUSION

In conclusion, the clinicians need to be aware of healthy subjects with tumor marker elevation over the upper limit of the normal range and the analytical differences of methods without missing diagnoses of malignant disease as well. Therefore, more attention should be paid to these subjects and further workup should be done to establish consensus guidelines for tumor marker(s) measurements.¹⁵ Each case may not have the same characteristics, and management should be individualized.

OBSERVATIONS

The abstract entitled "Unusual CA19-9 Elevation in a 37-year-old Mother and a 16-year-old Daughter" has been accepted as a poster presentation at the IFCC EUROMEDLAB Milano 2013 Congress. (19-23 May 2013).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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