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From interference to insight: pseudo-lipidemia led to the diagnosis of Waldenström macroglobulinemia

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Abstract

Waldenström macroglobulinemia (WM) is a rare hematological disorder with an annual incidence of about 3 per million. Its clinical manifestations are diverse and non - specific, and approximately 30% of patients are asymptomatic, making early diagnosis challenging. This paper reports a 73-year-old female who was admitted to the hospital due to atrial fibrillation. During a physical examination several years before the hospitalization, an elevated CA19-9 was detected, but the cause remained unclear after multiple outpatient visits. During cardiac markers testing, an abnormal serum index (HIL) suggested a lipidemic sample, yet the sample appeared clear visually. A Sia water test showed positive result, and subsequent serum protein electrophoresis confirmed the presence of M protein, leading to the diagnosis of WM. During the treatment in the following 6 years, it was found that the levels of CA19-9 and IgM fluctuated in parallel. Abnormal lipid indices and albumin-globulin ratio can provide important clues for the diagnosis of WM, but they may be overlooked in clinical practice. When the total protein increases with normal or decreased albumin levels, a reflex test of serum protein electrophoresis can help with early diagnosis. This case shows that understanding and using interference information in laboratory tests can assist in the diagnosis of WM.

Keywords Waldenström macroglobulinemia, Immunoglobulin M, CA19-9, Interference, Albumin - globulin ratio, Reflex test

Introduction

Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/W.M.) is an uncommon condition defined as the infiltration of the bone marrow by cells that produce monoclonal immunoglobulin M (IgM) [1] and has an annual incidence of approximately 3 per million [2–4].

Approximately 30% of patients with W.M. are asymptomatic, and the clinical presentation of W.M. is variable and non-specific, which includes weakness, uniqueness, and fatigue [5]. Patients with clinical presentation of W.M. have elevated monoclonal IgM levels and infiltration of bone marrow or other tissues by cells [1, 2, 5].

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Herein, we report a case of W.M. in a patient who was emergently admitted to the hospital owing to atrial fibrillation and whose elevated CA19-9 level was investigated for half a year in the outpatient department. The patient was finally diagnosed with W.M. with hints of an abnormal lipid index in a cardiac marker testing sample and was referred to the hematology department.

Case presentation

Ethics statement

This study was approved by the Ethics Committee of Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences (protocol number: K1533).

Case description

A 73-year-old woman presented to the Emergency Department with palpitations and syncope on September 2, 2014. Cardiogenic cardiac syncope may be higher after cardiovascular screening; thus, the patient was transferred to the Department of Cardiology for further treatment.The diagnosis and treatment history of the patient is presented in Fig. 1.

Myocardial markers were assessed during the patient's hospitalization in the Department of Cardiology. The analyzer system indicated a plasma index (HIL) of 114, suggestive of a lipidemic sample; however, visual inspection revealed that the plasma appeared clear. Consequently, Sia water tests were performed to investigate this discrepancy further. The mechanism underlying the water test is based on the principle that low ionic strength reduces the solubility of specific monoclonal immunoglobulins, leading to the formation of white flocculates. Elevated immunoglobulin levels were suspected following the water test results. Serum protein electrophoresis confirmed the presence of M protein. Based on these findings, the patient was subsequently referred to the Department of Hematology for further evaluation.

Before hospitalization, the patient had multiple visits to the Department of General Surgery and Gastroenterology at Peking Union Medical College Hospital due to elevated CA19-9 levels detected during a physical examination in 2014. The complete blood count was within normal limits. Laboratory results revealed total protein at 91 g/L (reference interval: 60–85 g/L), albumin at 41 g/L (reference interval: 35–52 g/L), and lactate dehydrogenase at 458 U/L (reference interval: 0–250 U/L). Imaging studies, including pancreatic-enhanced magnetic resonance imaging (MRI), gastrointestinal and gynecological ultrasonography, and abdominal-enhanced computed tomography, were unremarkable. Following the diagnosis of Waldenström's macroglobulinemia (WM), the patient received regular treatment. Notably, the CA19-9 level fluctuated in parallel with the IgM level.

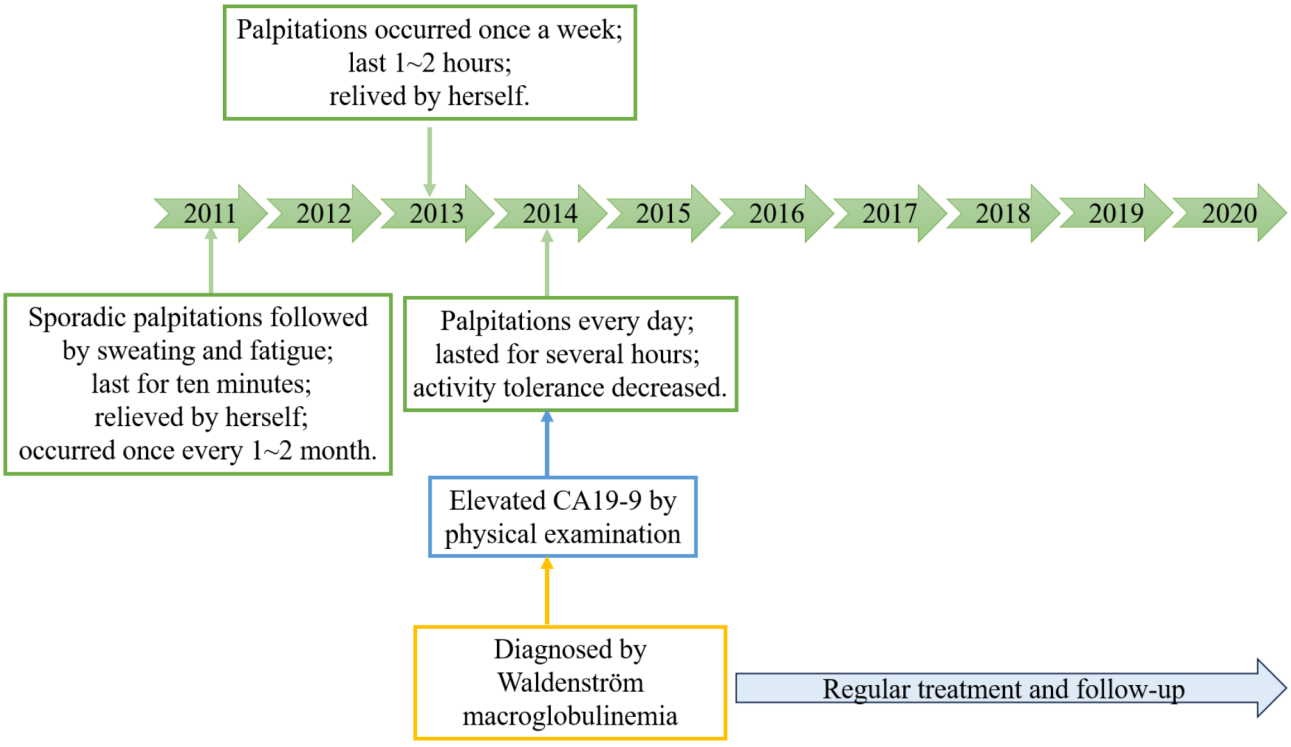

Fig. 1 The diagnosis and treatment history of the patient

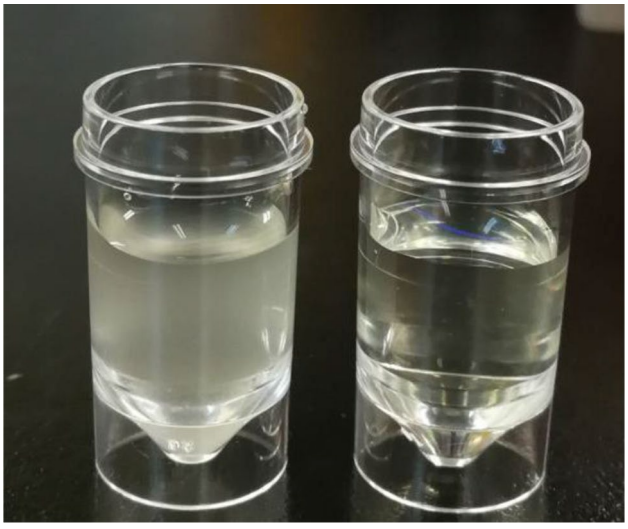

Fig. 2 Sia water test

Table 1 Serum protein electrophoresis

Index	Results	unit	variation	Reference interval
Alb(%)	29.8	%	↓	53.5–70.4
α1globulin	2.7	%	—	2.2–4.8
α2 globulin	6.0	%	—	5.4–11.1
β1globulin	6.0	%	—	4.1–7.3
β2 globulin	23.1	%	↑	1.8–6.2
γ globulin	32.4	%	↑	9.1–24.0
alb/globulin(A/G)	0.4		↓	1.0-2.5
M protein(%)	16.7	%	↑	0–0
M protein	16.30	g/L	↑	0–0

Note: The above results show the results of serum protein electrophoresis performed on September 9, 2014

Laboratory analysis

Sia water test: [6]

The Sia water test was conducted. One drop of plasma were added to 1.5 mL of distilled water. The results are presented in Fig. 2, where white flocculent sediment was observed on the left side. In contrast, the control group remained clear.

Serum protein electrophoresis

Serum protein electrophoresis (SPE) are shown in Table 1. M protein was 16.30 g/L (16.7%). Urine immunofixation electrophoresis (IFE) was weakly positive (F-κ), and serum immunofixation electrophoresis was IgM (κ). Serum light chain quantification indicated the following:κ/λ, 4.36; KAP, 6,110 mg/dL; and β_2 microglobulin, 7.070 mg/L, while urine light chain quantification was negative.

Bone marrow smear and biopsy

A bone marrow smear (Fig. 3) showed adequate cellular proliferation. The proportions and morphologies of granulated and erythroid systems were almost normal. Erythrocytes were arranged in a rouleaux formation. The proportions and morphologies of the lymphocytes, monocytes, and plasma cells were almost normal. Lymphoid plasma cells, accounting for 1% of the cells, were observed in the smears. Megakaryocytes and platelets are also observed.

Bone marrow biopsy: Hematopoietic tissue in the bone marrow tissue was reduced, the adipose tissue was relatively increased, the proportion of erythroids in hematopoietic tissue was normal, and megakaryocytes were present.

Immuno-histochemical results: CD138 (scattered +), CD20 (scattered +), CD3 (-), CD38 (scattered +), CD79 α (scattered +), kappa (+), lambda (+), MPO (+).

CA19-9 and IgM levels during treatment

During the treatment of WM from 2014 to 2020, the levels of CA19–9 and IgM fluctuated in parallel (Fig. 4).

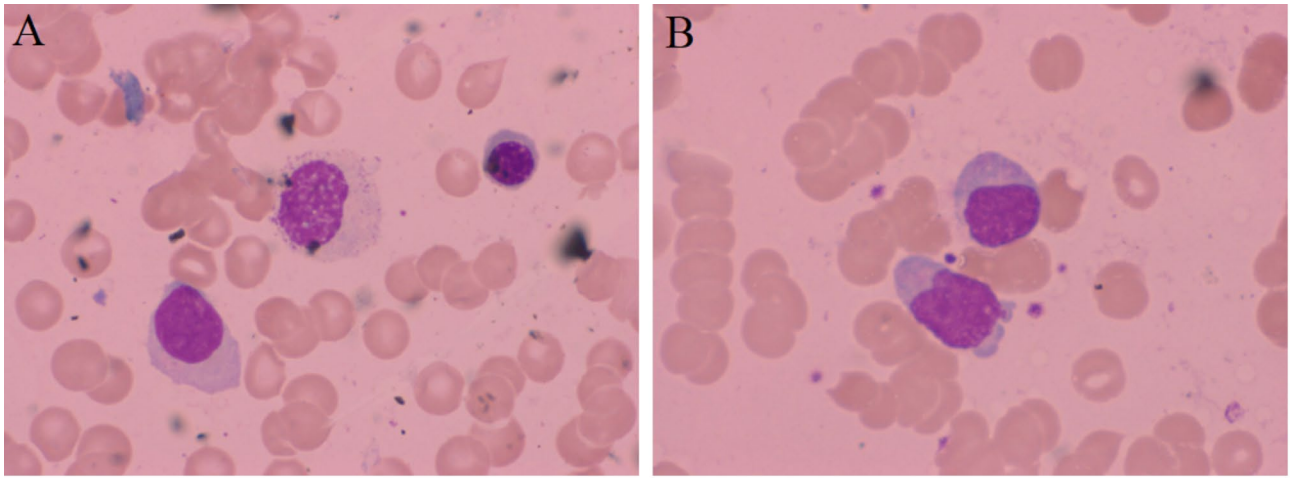

Fig. 3 Bone marrow smear

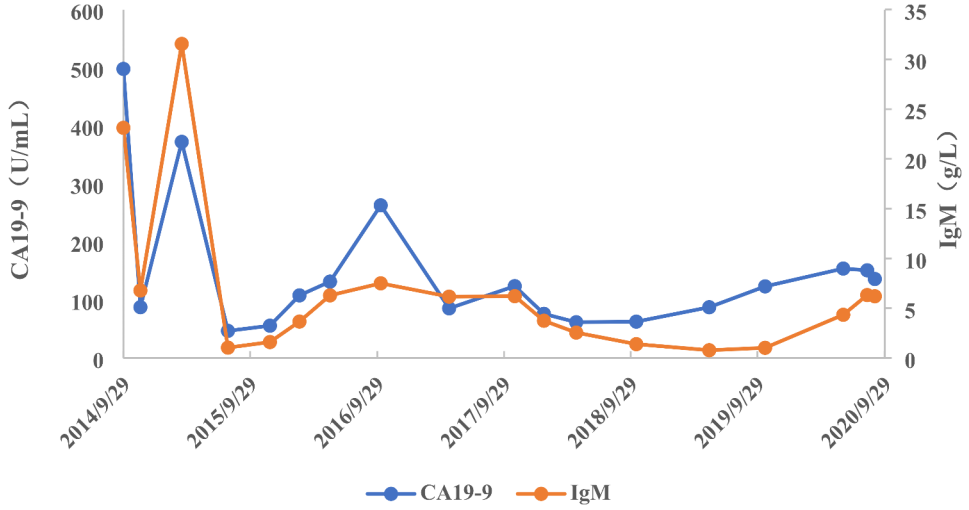

Fig. 4 Fluctuations in CA19–9 and IgM levels throughout the treatment

Discussion

The prevalence of W.M. is relatively low, and W.M. may have an asymptomatic course or present with symptoms and complications resulting from marrow or other tissue infiltration or physicochemical or immunological properties of monoclonal IgM [1]. In this case, the patient visited the hospital due to palpitations but was finally diagnosed with W.M. with hints of abnormal HIL during cardiac marker determination. Increased monoclonal IgM levels are the most prominent biochemical characteristic of WM. However, increasing macroglobulin cloud interference in some biochemical tests, such as ferritin, transferrin [7], creatinine [8], C-reactive protein (CRP) [9, 10], thyroid stimulating hormone [11], 25-hydroxy vitamin D [12], high-density lipoprotein cholesterol [13] and so on [14, 15].

Although higher macroglobulin levels interfere with the determination process, when we fully understand the information, we can convert the negative information into clinical diagnostic information to assist in the timely diagnosis of WM. In this case, the HIL results suggested a lipidemic sample, whereas the plasma was grossly clear. This conflict suggests that the testing process of the HIL may be affected. Sia water test was conducted to verify this process. The water became turbid when a drop of the patient's sample was added, whereas the control sample remained clear. Based on the positive sia-water result, an immunoglobulin test was performed, which revealed a very high IgM concentration.

Furthermore, serum protein electrophoresis and immunofixation electrophoresis were performed, which helped with the final diagnosis. In this case, clarifying the interference results helped to diagnose the patient accurately. Therefore, the interference is not always detrimental. In contrast, when we fully understand the interference mechanism, we can convert it into useful information to assist clinical diagnosis.

A decrease in total protein with albumin-globulin ratio (A/G) is another biochemical characteristic of WM. The patient visited the Department of General Surgery on May 12, 2014, to evaluate CA19-9, for the first time. The TP, Alb, and A/G were 91 g/L, 41 g/L, and 0.8, respectively. On July 14, 2014, after visiting the Department of Gastroenterology, a biochemical reporter showed that TP, Alb, and A/G were 95 g/L, 37 g/L, and 0.6, respectively. Unfortunately, the abnormalities in this biochemical report did not attract the attention of clinical and laboratory workers. Because the chief complaint of this patient was elevated CA19-9 levels, pancreatic-related issues were the primary consideration. However, pancreatic screening did not reveal any abnormalities. Unfortunately, a cost-effective and significant test, A/G, was ignored. A reflex test of serum protein electrophoresis should be suggested when TP increases with normal or decreased Alb level. Therefore, the patient could have received an accurate diagnosis several months earlier.

Another intriguing phenomenon noted in this study was the dynamic relationship between IgM and CA19-9 levels. CA19-9 is a widely utilized serum biomarker for diagnosing and monitoring gastrointestinal malignancies, particularly pancreatic cancer. Elevated serum CA19-9 levels have also been observed in two benign conditions: (1) inflammatory diseases of the digestive tract and liver, notably cholelithiasis, and (2) false-positive results potentially attributable to other interfering factors [16]. Our findings indicated a strong correlation between changes in CA19-9 levels and IgM concentrations. Before chemotherapy, IgM and CA19-9 levels were 23.12 g/L and 498 U/mL, respectively. After the first chemotherapy session, IgM decreased to 6.78 g/L, while CA19-9 significantly reduced to 88 U/mL. Six months later, IgM increased

to 31.55 g/L, and CA19-9 rose to 372 U/mL. Over the subsequent years, the patient's IgM concentrations fluctuated between 0.78 and 7.50 g/L, and CA19-9 levels ranged from 47 to 263 U/mL. During the initial visit, the patient underwent pancreatic-enhanced MRI, gastrointestinal ultrasonography, gynecological ultrasonography, and enhanced abdominal CT, all of which revealed no abnormalities. Throughout the follow-up period, no CA19-9-related diseases were detected.

Previous studies have reported that the false-positive result for CA19-9 might be correlated with interference, and the relevant causes of interference are the presence of rheumatoid factors, heterophilic antibodies, low molecular weight, and antibodies [16–20]. The solutions for managing clinical interference were: (1) using different detection systems, (2) linear dilution, (3) polyethylene glycol precipitation, and (4) a heterophilic antibody blocker. Unfortunately, this was a retrospective study, and we could not confirm this interference. Based on the parallel relationship between CA19-9 and IgM and the reported cases of macromolecular interference with CA19-9 in the literature, we speculate that the evaluated CA19-9 is related to IgM monoclonal globulin in this case.

In conclusion, this case report describes the diagnostic process of WM, in which a patient who was continuously evaluated for CA19-9 was finally diagnosed with W.M. due to pseudo-lipidemia caused by HIL during the treatment of atrial fibrillation. Moreover, this study suggests that using interference information during testing can aid in diagnosing W.M. The timely addition of SPE according to changes in TP and A/G is helpful for the timely diagnosis of WM. Furthermore, an asymptomatic increase in CA19-9 levels should be considered a possibility of interference.

Author contributions

Danchen Wang wrote the main manuscript, Liangyu xia reviewed and re-wrote the manuscript. Pengchang Li, Wei Su, Li'an Hou, Jianhua Han, Ying Zhang, Li Liu, Ling Qiu, and Danni Mu prepared the study and reviewed the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Consent for publication

This study was approved by the Ethics Committee of Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences (protocol number: K1533).

Competing interests

The authors declare no competing interests.

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References

1. Dimopoulos MA, Kastritis E. How I treat Waldenström macroglobulinemia. Blood. 2019;134:2022–35. https://doi.org/10.1182/blood.2019000725.
2. Fonseca R, Hayman S, Waldenström macroglobulinaemia. Br J Haematol. 2007;138:700–20. https://doi.org/10.1111/j.1365-2141.2007.06724.x.
3. Groves FD, Travis LB, Devesa SS, Ries LA, Fraumeni JF. Waldenström's macroglobulinemia: incidence patterns in the united States, 1988–1994. Cancer. 1998;82:1078–81. https://doi.org/10.1002/(SICI)1097-0142(19980315)82:6%3C1078::AID-CNCR10%3E3.0.CO;2-3.
4. Vijay A, Gertz MA, Waldenström macroglobulinemia. Blood. 2007;109:5096–103. https://doi.org/10.1182/blood-2006-11-055012.
5. Wang W, Lin P. Lymphoplasmacytic lymphoma and Waldenström macroglobulinaemia: clinicopathological features and differential diagnosis. Pathology. 2020;52:6–14. https://doi.org/10.1016/j.pathol.2019.09.009.
6. Krish P, Jhaveri KD. The case | hyperbicarbonatemia in a patient with Waldenstrom's macroglobulinemia. Pseudohyperbicarbonatemia due to paraproteinemia. Kidney Int. 2012;81:603–5. https://doi.org/10.1038/ki.2011.427.
7. Roszyk L, Faye B, Tournilhac O, Fogli A, Sapin V. [Monoclonal IgM interference with immunoturbidimetric determination of ferritin and transferrin]. Ann Biol Clin (Paris). 2007;65:659–62.
8. Salter T, Marsh J, Sood B, Livingstone C, Gallagher H. Pseudohypercreatininaemia in two patients caused by monoclonal IgM interference with enzymatic assay of creatinine. J Clin Pathol. 2015;68:854–5. https://doi.org/10.1136/jclinpath-2015-203064.
9. Yu A, Pira U. False increase in serum C-reactive protein caused by monoclonal IgM-lambda: a case report. Clin Chem Lab Med. 2001;39:983–7. https://doi.org/10.1515/CCLM.2001.160.
10. Gallou G, Legras B, Ruelland A, Grosbois B, Cloarec L. Problems of C-reactive protein determination in patients with monoclonal Immunoglobulins. Clin Chem. 1993;39:918. https://doi.org/10.1093/clinchem/39.5.918.
11. Imperiali M, Jelmini P, Ferraro B, Keller F, della Bruna R, Balerna M, Giovanella L. Interference in thyroid-stimulating hormone determination. Eur J Clin Investig. 2010;40:756–8. https://doi.org/10.1111/j.1365-2362.2010.02315.x.
12. Whittle E, de Waal E, Huynh T, Treacy O, Morton A. Pre-analytical mysteries: A case of severe hypervitaminosis D and mild hypercalcaemia. Biochem Med (Zagreb). 2021;31:011001. https://doi.org/10.11613/BM.2021.011001.
13. Shahbaz A, Aziz K, Umair M, Zarghamravanbakhsh P, Sachmechi I. A patient with artifactually low serum high density lipoprotein cholesterol due to Waldenstrom macroglobulinemia. Cureus. 2018;10:e2900. https://doi.org/10.7759/cureus.2900.
14. Granouillet R, Rascle F, Bonneau C, Chamson A, Frey J, Perier C. Evidence of temperature-dependent interference in an immunonephelometric assay by monoclonal IgM. Clin Chem. 1999;45:2039–40. https://doi.org/10.1093/clinchem/45.11.2039.
15. King RI, Florkowski CM. How paraproteins can affect laboratory assays: spurious results and biological effects. Pathology. 2010;42:397–401. https://doi.org/10.3109/00313025.2010.493868.
16. Galli C, Basso D, Plebani M. CA, CA 19–9: handle with care. Clin Chem Lab Med. 2013;51:1369–83. https://doi.org/10.1515/cclm-2012-0744.
17. Zhao W, Duan L, Fang L, Li J, Li S, Wang L, Zhang J, Zhang W, Cao Y. Persistent increase of carbohydrate antigen 19–9 with an unknown reason: A seven-year follow-up case. J Clin Lab Anal. 2022;36:e24792. https://doi.org/10.1002/jcla.24792.
18. Liang Y, Yang Z, Ye W, Yang J, He M, Zhong R. Falsely elevated carbohydrate antigen 19–9 level due to heterophilic antibody interference but not rheumatoid factor: a case report. Clin Chem Lab Med. 2009;47:116–7. https://doi.org/10.1515/CCLM.2009.020.
19. Berth M, Bosmans E, Everaert J, Dierick J, Schiettecatte J, Anckaert E, Delanghe J. Rheumatoid factor interference in the determination of carbohydrate antigen 19–9. Clin Chem Lab Med. 2006;44:1137–9. https://doi.org/10.1515/CCLM.2006.205. (CA 19–9.

20. Monaghan PJ, Leonard MB, Neithercut WD, Raraty MG, Sodi R. False positive carbohydrate antigen 19–9 (CA19-9) results due to a low-molecular weight interference in an apparently healthy male. Clin Chim Acta. 2009;406:41–4. https://doi.org/10.1016/j.cca.2009.05.012.

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