

Teaching Case

Heterophilic Antibodies Resulting in False Positive Elevation of PSA After Radical Prostatectomy

Wafa Asha, MD,^a Elizabeth Obi, MD,^b and Rahul Tendulkar, MD^{b,*}^aDepartment of Radiation Oncology, King Hussein Cancer Center, Amman, Jordan; and ^bDepartment of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio

Received 21 January 2023; accepted 5 June 2023

Case Report

A 63-year-old man with prostate cancer underwent a radical prostatectomy, and final pathology revealed Gleason 7(4+3) adenocarcinoma with negative surgical margins. His prostate specific antigen (PSA) remained undetectable for 15 years, until his PSA was found to be suddenly elevated at 0.7 ng/mL; a repeat PSA was 0.6 ng/mL. A restaging prostate-specific membrane antigen positron emission tomography-computed tomography scan revealed no evidence of local recurrence or distant metastasis. The patient was referred for salvage pelvic radiation therapy with androgen deprivation therapy. Because of the unusual and sudden nature of the PSA elevation, a spurious PSA elevation caused by interference of heterophilic antibodies was suspected. Repeat PSA testing with human antimouse antibodies treatment revealed the PSA to be <0.02 ng/mL, compared with 0.41 ng/mL in the uncorrected sample.

Discussion

Human antibodies against animal antibodies, also known as “heterophilic antibodies,” are commonly identified in humans and are thought to arise from exposure to animals or animal serum products, such as in immunoglobulin

therapy.¹ Heterophilic antibodies can interfere with a variety of immunoassays for tumor markers (such as PSA, human chorionic gonadotropin, α -fetoprotein, cancer antigen 125, and calcitonin), infectious diseases, hormones, drugs, and cardiac markers (such as troponin-I), leading to false positive results, with an estimated incidence of 0.05%.² To neutralize heterophilic antibody interference, a blocking reagent must be incorporated with the assay.^{2,3}

In this case report, we describe an unusual case of a spurious elevation of PSA caused by heterophilic antibodies. After a radical prostatectomy, PSA levels should be undetectable if all prostate tissue has been surgically removed. Patients with residual prostate cancer will typically have a systematic rise in PSA over time but would not be expected to have a sudden rise after 15 years with an undetectable PSA level. As such, we suspected a false elevation, and repeating the PSA assay with a blocking reagent prevented this patient from unnecessary overtreatment. Prior case reports have been published regarding false elevations of PSA caused by heterophilic antibodies,^{4,5} including some cases where an unnecessary salvage treatment was performed.^{6–11} Unfortunately, the presence of heterophilic antibodies can pose diagnostic challenges for medical laboratories, and the rare nature of this issue may not be widely known in the medical field. Before seeking our opinion, this patient had been recommended to undergo pelvic irradiation with hormonal therapy at another facility. This treatment is associated with side effects, financial cost, and a long treatment duration. In situations in which the clinical suspicion of recurrent prostate cancer is low, repeating the PSA with heterophilic antibody blocking reagents is recommended to rule out a spurious elevation.

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Corresponding author: Rahul Tendulkar, MD; E-mail: tendulr@ccf.org

<https://doi.org/10.1016/j.adro.2023.101288>

2452-1094/© 2023 The Authors. Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Conclusion

The presence of heterophilic antibodies can cause falsely positive elevation in PSA, which can lead to patient anxiety and costly, unnecessary salvage treatments. When the suspicion of recurrent prostate cancer is low, repeating the PSA with antibody blocking reagents is recommended to verify that the PSA is not spuriously elevated.

Disclosures

Rahul Tendulkar reports receiving honoraria from Varian Medical Systems. All other authors have no disclosures to declare.

References

1. Levinson SS. Antibody multispecificity in immunoassay interference. *Clin Biochem.* 1992;25:77-87.
2. Levinson SS, Miller JJ. Towards a better understanding of heterophile (and the like) antibody interference with modern immunoassays. *Clin Chim Acta.* 2002;325:1-15.
3. Kricka LJ. Human anti-animal antibody interferences in immunological assays. *Clin Chem.* 1999;45:942-956.
4. Park S, Wians Jr FH, Cadeddu JA. Spurious prostate-specific antigen (PSA) recurrence after radical prostatectomy: Interference by human antimouse heterophile antibodies. *Int J Urol.* 2007;14:251-253.
5. Poyet C, Hof D, Sulser T, Muntener M. Artificial prostate-specific antigen persistence after radical prostatectomy. *J Clin Oncol.* 2012;30:e62-e63.
6. Fritz BE, Hauke RJ, Stickle DF. New onset of heterophilic antibody interference in prostate-specific antigen measurement occurring during the period of post-prostatectomy prostate-specific antigen monitoring. *Ann Clin Biochem.* 2009;46(Pt 3):253-256.
7. Morgan BR, Tarter TH. Serum heterophile antibodies interfere with prostate specific antigen test and result in over treatment in a patient with prostate cancer. *J Urol.* 2001;166:2311-2312.
8. Kummur S, Shafi NQ. False elevations in prostate-specific antigen levels affecting patient management. *Clin Adv Hematol Oncol.* 2004;2:599-601. discussion 602.
9. Camacho T, Mora J, Segura A, et al. Falsely increased prostate-specific antigen concentration attributed to heterophilic antibodies. *Ann Clin Biochem.* 2002;39(Pt 2):160-161.
10. Henry N, Sebe P, Cussenot O. Inappropriate treatment of prostate cancer caused by heterophilic antibody interference. *Nat Clin Pract Urol.* 2009;6:164-167.
11. Dominguez A, Bayo M, Munoz-Rodriguez J, et al. Repeated spurious elevation of serum prostate-specific antigen values solved by chemiluminescence analysis: A possible interference by heterophilic antibodies. *Korean J Urol.* 2015;56:785-787.