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A Common, Under-Recognized Cause of Elevated Serum Erythropoietin

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To the Editor

When evaluating etiologies of erythrocytosis, serum erythropoietin is used to distinguish polycythemia vera from secondary causes. Paraneoplastic polycythemia is a rare cause of secondary polycythemia, most frequently associated with renal cell or hepatocellular carcinomas. This diagnosis should be considered in patients with erythrocytosis and an inappropriately-normal or high erythropoietin, in the absence of physiologic stimuli for erythropoietin overproduction.

Case Summary

A 49-year-old man was incidentally found to have an elevated hemoglobin of 17.1 grams/dL (reference 12.5–17.0 grams/dL) and hematocrit of 51.5% (reference 36–50%).

Erythropoietin level was markedly elevated at 171 mIU/mL (reference 4.2–27.8 mIU/mL).

The patient had no history of hypoxia, tobacco use, and no family history of cancer,

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hemoglobinopathies, or genetic disorders. He was taking no medications. On physical exam, he was normotensive, with normal oxygen saturation, and no abnormal physical findings. Although subsequent studies showed hemoglobin in the high-normal range, erythropoietin remained markedly elevated (92.5–189 mIU/mL). To evaluate for an occult renal or renovascular source, renal venous sampling was performed, with similarly elevated erythropoietin levels bilaterally. Magnetic resonance imaging (MRI) of the abdomen showed no renal, adrenal or liver masses; positron emission tomography-computed tomography (PET-CT) was similarly unrevealing. Brain MRI showed no evidence of cerebellar hemangioblastoma. No Erythropoietin Receptor or Von Hippel-Lindau gene mutations were found.

Serendipitously, our institution's laboratory was transitioning between two commercial erythropoietin assays widely-used in the United States, both of which employ antibody-based capture to measure erythropoietin(1). To ensure assay reproducibility, the lab tested samples from 126 patients with both assays, and two patients, including ours, showed widely discrepant results. While the patient's erythropoietin was abnormally high with one immunoassay(1), it was normal with the other assay. Maneuvers to assess for heterophile and human anti-animal antibody interference with linear dilutions and blocking agents failed to resolve the discrepancy. There was no interfering serum paraprotein. To measure erythropoietin using another technology, the sample was sent for protein electrophoresis to an independent laboratory specializing in "blood doping"; active erythropoietin species were confirmed to be normal, affirming that the high measurements were spurious. A review of the patient's four-year-long evaluation confirmed that all prior erythropoietin levels measured by two independent, major commercial laboratories as well as our own were performed using the same clinical immunoassay, consistently producing falsely-elevated results.

Discussion

Although heterophile antibody and other nonspecific interference are a widely acknowledged limitation of immunoassays in the laboratory medicine community(2), it is under-recognized by internists. Many routine clinical screening tests, such as hormone levels, viral serologies, tumor markers, and biomarkers of cardiac injury may be affected by assay interference, potentially leading to unnecessary procedures, anxiety, expense, and patient harm(3)(Table 1). A physician should suspect an erroneous result if it contradicts the clinical presentation; however, a false result of an appropriately-ordered test may well be compatible with the clinical history, and may be less likely to engender skepticism. Confirmation with alternative technologies should be sought, recognizing that it may not be possible or practical in all cases. Our laboratory found discrepant erythropoietin results in two of 126 samples, consistent with the one per 98 samples heterophile interference rate in the study that established this assay as suitable for routine clinical use(1). *The 1% assay interference rate makes false-positive results a far more common cause of elevated erythropoietin than an occult erythropoietin-producing tumor.* Our case highlights the need for greater safeguards for tests employed in routine clinical practice, and calls for improved result reporting to increase the awareness of assay limitations among clinicians.

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Table 1

Common Clinical Immunoassays Known to be Affected by Heterophile Antibody Interference

Hormones	Tumor Markers
Adrenocorticotropin Hormone (ACTH)	Alpha fetoprotein (AFP)
Calcitonin	Cancer Antigen 125 (CA 125)
Cortisol	Cancer Antigen 19-9 (CA 19-9)
Erythropoietin	Carcinoembryonic Antigen (CEA)
Follicular Stimulating Hormone (FSH)	Chromogranin A
Growth Hormone (GH)	Human Chorionic Gonadotropin (HCG)
Human Chorionic Gonadotropin (HCG)	Prostate-Specific Antigen (PSA)
Inhibin A	
Luteinizing hormone (LH)	Drug Levels
Parathyroid Hormone (PTH)	Digoxin
Prolactin	Tacrolimus
Serum Antimüllerian Hormone (AMH)	
Testosterone	Autoimmune Serologies
Thyroglobulin	Anti-dsDNA antibodies
Thyroid-Stimulating Hormone (TSH)	
Thyroxine	Viral Serologies
	Hepatitis B Antigen
Other Tests	Human Immunodeficiency Virus (HIV) Serologies
Ferritin	
Myoglobin	Markers of Myocardial Injury
Tryptase	Creatine Kinase-MB (CK-MB)
	Troponin-I