CASE REPORT

Heterophile Antibody to Adrenocorticotropin Hormone Interfering with the Investigation of Cushing's Syndrome

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Abstract The practice of medicine depends on the accuracy of biochemical assays. The high prevalence of incidental masses on imaging necessitates a correct biochemical diagnosis before proceeding to radiological studies. Hormonal assays, tumour markers, and markers of cardiac injury are particularly susceptible to heterophile antibody interference which may lead to inaccurate and misleading results, inappropriate investigation and/or treatment, patient concern and potential harm. A case of heterophile antibody interference in the measurement of ACTH in a patient with Cushing's syndrome resulting in unnecessary invasive investigation is presented. Close collaboration and communication between laboratory and clinical staff is essential where laboratory results and the clinical picture are not congruent.

Keywords Heterophile antibody · ACTH · Cushing's syndrome

Case Report

A 54 year old man was referred for investigation of abnormal liver function tests. The patient's medical history was significant for obesity, hypertension, osteoporosis, obstructive sleep apnoea, epilepsy and primary hypogonadism. On examination facial plethora, easy bruising, thin skin, proximal myopathy and cutaneous striae were

suggestive of Cushing's syndrome (CS). Twenty-four hour urine free cortisol was 607 nmol/day (normal < 150) and serum adrenocorticotropin hormone (ACTH) was 14.4 pmol/L (1.5–11) on an Immulite assay consistent with ACTH dependent CS.

Serum cortisol and ACTH failed to suppress with 8 mg of dexamethasone, performed while the patient was taking primidone and carbamazepine. Magnetic resonance imaging (MRI) of the pituitary was normal. Inferior petrosal sinus sampling showed an absent central to peripheral venous gradient for ACTH. Computerised tomography (CT) of the chest and abdomen looking for an ectopic source of ACTH revealed a 32 mm well-defined adrenal mass of 25 Hounsfield units (Fig. 1). Plasma metanephrines and aldosterone: renin ratio were normal. Measurement on a Roche e170 analyser revealed an ACTH level of 0.2 pmol/L consistent with an interferent in the Immulite assay. The adrenocortical adenoma was removed laparoscopically, with clinical and biochemical resolution of CS.

Discussion

Heterophile antibodies may affect a wide array of laboratory tests, resulting in false elevation of endocrine assays, tumour markers, markers of cardiac injury and drug levels (Table 1) [1]. Numerous case reports describe patients having unnecessary chemotherapy, procedures and surgery based upon incorrect results due to heterophile antibody interference. Heterophile antibodies may also cause false depression of serum cortisol and thyroglobulin. Analytically important heterophile antibodies are estimated to occur in 0.5–3% of specimens [2]. Two-site immunometric or sandwich assays are particularly susceptible to analytical error with heterophile antibodies. The presence of

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Fig. 1 CT abdomen demonstrating right adrenal adenoma

heterophile antibodies interfering with the accuracy of investigations can be addressed through analysis by an alternative analytical platform, non-linearity of results on serial dilution, polyethylene glycol precipitation or the use of heterophile or immunoglobulin-blocking reagents. More than one of these methods may be required.

One previous case report described heterophile antibody to ACTH in the setting of ACTH-independent CS. Grasko

et al. [3] reported a 60 year old woman with CS with ACTH levels ranging between 3 and 6 pmol/L when assayed on the siemens immulite 2000Xpi analyser by solid-phase two-site sequential enzyme immunoassay with a chemiluminescent substrate. MRI revealed central nodular bulkiness of the pituitary without a discrete adenoma and inferior petrosal sinus sampling showed an absent central to peripheral venous gradient for ACTH. CT scan of the abdomen showed bilateral adrenal enlargement, and adrenal vein sampling suggested predominant right-sided production of cortisol. Plasma ACTH was below the lower limit of detection when assayed by an alternative method, Roche Elecsys E170. The patient proceeded to adrenalectomy with normalization of serum and urine cortisol levels. Choy et al. [4] described a woman with CS who underwent completion hypophysectomy because of a persistent elevation of ACTH on a siemens immulite analyser after removal of a pituitary adenoma staining strongly for ACTH at initial transphenoidal left hemi-hypophysectomy. Serial dilution was non-linear, and ACTH level was low on a Roche Cobas e602 analyzer. Two further case reports describe heterophile antibodies interfering with ACTH measurement and clinical management [5] [6]. In a series of 437 patients with incidentally discovered

Table 1 Immunoassays potentially affected by heterophile antibodies

Cardiac markers

Troponin, creatine kinase-MB isoenzyme, B-type natriuretic peptide (BNP)

Tumour markers

Prostate-specific antigen (PSA)

Carcinoembryonic antigen (CEA), cancer antigen 19–9 (CA 19–9), cancer antigen 125 (CA 125)

Alpha-fetoprotein (AFP), beta human chorionic gonadotropin (βhCG)

Calcitonin

Thyroglobulin

Chromogranin A

Endocrine tests

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, oestradiol, progesterone, testosterone

Thyroid-stimulating hormone (TSH), free thyroxine (FT4), Free triiodothyronine (FT3)

Adrenocorticotrophic hormone (ACTH), cortisol

Parathyroid hormone (PTH)

Inhibin A

Drug levels

Digoxin

Cyclosporine, tacrolimus

Other

Tryptase

Myoglobin

Antiphospholipid antibodies

Erythropoietin

Human immunodeficiency virus (HIV)

adrenal adenomas who were investigated for subclinical CS, antibodies causing analytical interference with measurement of ACTH affecting clinical management were detected in 4 individuals [7].

Conclusion

In conclusion a case of heterophile antibodies causing false elevation of ACTH and misleading the diagnostic workup of CS is described. In our case and that described by Grasko et al., interference with analysis of ACTH levels led to unnecessary inferior petrosal sinus sampling. More seriously in the case presented by Choy et al., heterophile antibody interference prompted unnecessary completion hypophysectomy and the risk of panhypopituitarism requiring lifelong hormone replacement therapy. Physicians should be aware of the possibility of heterophile antibodies interfering with assays particularly where the clinical picture does not correlate with biochemical results. Close communication and collaboration between the clinician and laboratory is paramount.

Compliance with Ethical Standards

Conflict of interest Adam Morton and Tom Dover declare that they have no conflict of interest.

Informed Consent The patient gave signed informed consent for publication of the manuscript.

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