Cancer Immunotherapies and Endocrine Dysfunction

Cancer immunotherapies can unmask or precipitate disorders of endocrine glands. Thyroid dysfunction is by far the most common endocrinopathy in this context, although more rarely hypophysitis, Addison’s disease and Type 1 diabetes can occur.

Thyroid Disorders

Approximately 5-10% of individuals treated with cancer immunotherapies will develop abnormal thyroid function and this may be either thyrotoxicosis or hypothyroidism. Immunotherapies may cause a destructive thyroiditis or precipitate the presentation of Graves’ disease or autoimmune hypothyroidism. Patients with pre-existing thyroid antibodies are at increased risk. Thyroiditis usually occurs during the first few cycles of therapy and the typical pattern is of transient hyperthyroidism followed by hypothyroidism.

Interpretation of Thyroid Function Tests

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| TSH(0.2-4.5 mU/l) | fT4(9-21 pmol/l) | fT3(2.6-6.2 pmol/l) | Interpretation |
| <0.01 | >21 | >6.2 | Thyrotoxicosis |
| <0.01 | High normal | >6.2 | T3 thyrotoxicosis |
| <0.01 | High normal | High normal | Subclinical thyrotoxicosis |
| <0.01 | <9 | <2.6 | Secondary hypothyroidism (pituitary cause) |
| <0.01 | Low normal | Low normal | Subclinical secondary hypothyroidism (pituitary cause) |
| >4.5 | <9 | <2.6 | Primary hypothyroidism |
| >4.5 | Low normal | Low normal | Subclinical primary hypothyroidism |

It is very important that low TSH levels are interpreted along with T4 and T3 levels, because a low TSH can occur in both thyrotoxicosis and secondary hypothyroidism.

Suggested monitoring

* TSH and fT4 should be checked prior to commencement of the immunotherapy.
* If TFTs are abnormal then these results should be discussed with an endocrinologist before the immunotherapy is started.
* TSH and fT4 should be checked at least monthly while on the immunotherapy; after 6 months, the monitoring frequency can reduce to 3 monthly if the patient is asymptomatic. New symptoms, which could be indicative of thyroid dysfunction, should prompt earlier assessment of thyroid function. fT3 should be added on if TSH is low and fT4 high normal.

Investigation and Management of Thyrotoxicosis

* Thyrotoxicosis should be detected biochemically before symptoms occur.
* Most commonly this will be due to a destructive thyroiditis, in which case it should be self-limiting over a few weeks or months. It is not mandatory to stop the immunotherapy, but it is likely that cessation of therapy will speed resolution of the thyrotoxicosis. If the immunotherapy is to be continued, the case should be discussed with an Endocrinologist.
* If symptomatic, commence Propranolol (20-80 mg t.d.s) and continue until T4 normal. Inderal LA is a once daily preparation of Propranolol and is very useful – it is available in 80mg and 160 mg preparations and is administered once daily.
* Measure TRAb titres (TSH Receptor Antibodies – brown tube to Clinical Biochemistry). Positive TRAbs confirms a diagnosis of Graves’ disease.
* If TRAbs are negative, arrange a thyroid scintigram with Nuclear Medicine.
* If thyroiditis confirmed, monitor TFTs every 4 weeks, watching out for development of hypothyroidism.
* Neck pain can be treated with NSAIDS.
* Severe episodes of thyroiditis (i.e. significant neck pain and/or thyrotoxicosis) may require additional therapy with Prednisolone (40mg daily) until T4 is normal.
* If TRAbs are positive or the thyroid scintigram shows evidence of Graves’ disease or nodular disease, refer to Endocrinology

Management of Hypothyroidism

* Hypothyroidism detected *de novo* may be due to autoimmune disease or, more commonly, is the tail-end of an episode of thyroiditis in which the hyperthyroid phase was not clinically evident.
* If TSH >10 and/or T4 <9, commence Levothyroxine 100 ug/daily. If elderly or have pre-existing cardiac disease, discuss with Endocrinologist as a lower starting dose should be used.
* If TSH 5-10 and T4 >9, treatment may not be necessary, unless symptomatic
* Recheck TFTs after 4 weeks and adjust T4 dose according to TSH
* It is usually not necessary to discontinue the immunotherapy when hypothyroidism is detected *de novo*.
* Hypothyroidism may not be permanent. After 4-6 months of Levothyroxine therapy, it is always worth reducing the dose to 50 mcg. If TSH is in the normal range 4 weeks later, discontinue the Levothyroxine and recheck TFTs after another 4 weeks. An elevated TSH at any stage indicates an on-going requirement for Levothyroxine. The risk of permanent hypothyroidism will be higher in those with positive anti-thyroid peroxidase antibodies.

Hypophysitis

Immunotherapy can activate an autoimmune, inflammatory process within the pituitary – lymphocytic hypophysitis. This can cause hypopituitarism, which may in turn result in hypoadrenalism. The symptoms are non-specific but include:

* Fatigue
* Postural dizziness
* Weight gain
* Low mood
* Headache
* Visual field disturbance (rare)
* Thirst, poluyuria, polydipsia

Dilutional hyponatraemia/SIADH may be caused by cortisol deficiency; therefore hypophysitis should always be considered in any patient with hyponatraemia.

Investigation and Management of Lymphocytic Hypophysitis

* Routine monitoring for hypophysitis is not indicated, but there should be a high index of suspicion. If lymphocytic hypophysitis is suspected, U&Es, TSH, T4 and a random cortisol should be measured in the first instance (where possibly in an early morning sample, but this is not essential).
* If there is a high index of suspicion of lymphocytic hypohysitis, commence hydrocortisone 20mg mane; 10mg at 6pm; intravenous hydrocortisone 100mg 6hrly should be given if the patient is very unwell.
* All cases of suspected lymphocytic hypophysitis should be discussed with an endocrinologist.
* Interpretation of the random cortisol levels can be tricky. A cortisol level of >430 nmol/l is normal. Levels below this may be normal depending on the sampling circumstances and whether the patient is receiving steroids. A short synacthen test (SST) may be falsely normal in acute lymphocytic hypophysitis, but is a useful test if the hypophysitis is more longstanding (several weeks duration). Ideally a SST should be performed prior to initiation of hydrocortisone, but this may not be practically possible and it is better to start the hydrocortisone than unnecessarily delay treatment.
* Remember that TSH may be inappropriately low or ‘normal’ in hypothyroidism of pituitary origin, so T4 is the key measure.
* Thirst, polyuria and polydipsia may be indicative of diabetes insipidus, but diabetes mellitus and hypercalcaemia should be excluded.
* If lymphocytic hypophysitis is suspected on the initial blood screen, further hormone investigation can be co-ordinated by endocrinology and may include LH, FSH, Testosterone (in men) and Prolactin. A pituitary MRI will be required to exclude hypopituitarism secondary to a pituitary metastasis and to determine if there is any threat to the optic chiasm.
* Some oncology protocols recommend high dose Dexamethasone if lymphocytic hypophysitis. There are no convincing data that this alters the natural history, i.e. reduces the likelihood of long-term pituitary dysfunction. However, if there is a significant inflammatory mass that is causing headache and/or visual disturbance then high dose Dexamethasone should be commenced, but early discussion with an endocrinologist is recommended.

**Addison’s Disease**

Addison’s disease is rare in this context. Symptoms are again vague and there is overlap with some of the symptoms of hypophysitis. The key symptoms are:

* Fatigue
* Low mood
* Weight loss
* Postural hypotension
* Increased pigmentation – especially of surgical scars, skin creases

The classical biochemical picture of hyponatraemia and hyperkalaemia is not always seen in Addison’s disease, but their presence should mandate further investigation.

Investigations

* Routine screening for Addison’s disease is not indicated. The same initial screen as for hypophysitis should be performed. The cortisol results should be discussed with an endocrinologist.
* Treatment with Hydrocortisone should be commenced as above, if there is a high index of suspicion.

**Type 1 diabetes**

Type 1 diabetes is very rare in this context, but should be suspected in anyone with osmotic symptoms (thirst, polyuria and polydipsia) and weight loss. There should be a low threshold for checking glucose in an individual with such symptoms; urine should also be dipped for ketones. The finding of an elevated glucose and ketonuria should prompt an urgent discussion with the endocrine team

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