



Pomalidomide-induced hypothyroidism

Sulaiman Haji Ali¹, K Aljenaee², W A Wan Mahmood¹ and M Hatunic^{1,3}

¹Endocrinology Department, Mater Misericordiae University Hospital, Dublin, Ireland, ²Endocrinology Department, Connolly Hospital, Dublin, Ireland, and ³University College Dublin, Dublin, Ireland

Correspondence
should be addressed
to S H Ali
Email
Dr.sulaimanhaji@hotmail.com

Summary

Hypothyroidism is a recognized side effect of thalidomide drugs. We herein report a case of 83-year-old Irish female with a diagnosis of multiple myeloma and a background history of type 2 diabetes mellitus and hypertension. Our patient received pomalidomide and multiple courses of chemotherapy and achieved very good initial response for her multiple myeloma but subsequently she relapsed. She did not have any past history of thyroid disease or family history of thyroid disorders. Prior to treatment with pomalidomide, her thyroid function test was completely normal. She was commenced on pomalidomide in February 2017. Four weeks post treatment, she presented with worsening fatigue, and as a part of her workup, a thyroid function test was performed. Her free T4 was low at 7.2 pmol/L (reference range: 9.0–20.0) while her TSH was elevated at 44.7 mIU/L (reference range: 0.35–4.94). Pomalidomide treatment was terminated, and she was commenced on thyroid hormonal therapy replacement therapy with thyroxine with good clinical and biochemical response. Practitioners prescribing pomalidomide should be aware of this potential complication and patients who are receiving immunomodulatory drugs like pomalidomide should undergo regular thyroid hormone levels screen.

Learning points:

- Overt hypothyroidism is a side effect of pomalidomide.
- Thyroid function test should be included as a screening test with regular review in patients receiving pomalidomide.
- Unexplained worsening fatigue in patients receiving pomalidomide should raise the possibility of overt hypothyroidism.

Background

Hypothyroidism is a recognized side effect of thalidomide drugs. We herein report a case of 83-year-old Irish female with a diagnosis of multiple myeloma and a background history of type 2 diabetes mellitus and hypertension.

Case presentation

An 83-year-old female with a background history of type 2 diabetes mellitus for 25 years complicated by diabetic retinopathy and hypertension was diagnosed with IgG kappa multiple myeloma in September 2011. She presented with gradual onset of malaise, anorexia and fatigue. Her investigation showed normocytic anemia (hemoglobin

level of 10.1 (g/dL) (reference range: 12.3–15.3 g/dL) with an elevated ESR of 112 mm/h (reference range: 1–20 mm/h). Colonoscopy investigation was normal, and she was referred to the hematology department for further investigations. Serum protein electrophoresis (SPEP) revealed a high-normal serum total protein of 80 g/L (reference range: 60–80 g/L), with elevated serum globulin (45 g/L, reference range: 18–36 g/L) and IgG level (24.20 g/L, reference range: 7.00–16.00 g/L). Additionally investigation showed, serum light chain elevated kappa light chain (98.0 mg/L, reference range: 3.3–19.4 mg/L), normal lambda light chain (7.8 mg/L, reference range: 5.71–26.3 mg/L), with an elevated kappa-to-lambda



ratio (12.564, reference range: 0.310–1.200). Beta 2 microglobulin was normal, and her urine was negative for Bence Jones protein (BJP). A skeletal survey revealed no lytic lesions and a bone marrow aspirate and trephine biopsy revealed 10–15% plasma cells, stained positive for CD138. She had elevated serum urea (12.9 mmol/L (reference range: 2.8–8.6 mmol/L)) and Creatinine level (112 µmol/L (reference range: 46–86 µmol/L)) with normal calcium and albumin levels.

Our patient was commenced on 6 cycles of cyclophosphamide, thalidomide and dexamethasone (CTD) between September 2011 and March 2012 and achieved a very good partial response, but unfortunately relapsed in 2013. She was treated with bortezomib and dexamethasone followed by cyclophosphamide, bortezomib and dexamethasone (CyBORd) for 6 cycles and achieved a good response. Unfortunately, she had a second relapse in February 2016, whereby she was treated with one cycle of lenalidomide and prednisolone. Lenalidomide was discontinued in March 2016 due to acute kidney injury. She was recommenced on bortezomib and prednisolone for another 5 cycles but her response was poor. In February

2017, she was commenced on pomalidomide 3 mg. She had normal thyroid function test prior to pomalidomide treatment. After 4 weeks of initiation of pomalidomide, she presented with worsening fatigue. Our patient had not had any family history of thyroid disorder. Her clinical examinations were normal including no palpable goiter or lymphadenopathy. Her thyroid function test revealed profound hypothyroidism with low fT4 at 7.2 (pmol/L) (reference range: 9.0–20.0 pmol/L) and an elevated TSH at 44.7 mIU/L (reference range: 0.35–4.94 mIU/L). She was reviewed by the endocrinology specialty and was commenced on levothyroxine 50 µg daily and dose was increased to 100 µg daily over four weeks. Her thyroid peroxidase antibody (TPO Ab) was – positive 405.8 IU/mL (reference range <5.6). Thyroid ultrasound showed heterogeneous thyroid gland, which suggestive of thyroiditis with no evidence of lymphadenopathy or suspicious nodules. Our patient was reviewed recently in endocrinology outpatient department with a good clinical and biochemical response and recent thyroid function test was normal, a FT4 of 14.2 pmol/L and TSH 1.10 mIU/L.

Table 1 Antineoplastic and thyroidal dysfunctions.

Agent	Likely mechanism of effect on thyroid	Clinical manifestations	Average time from first exposure to onset	Frequency of thyroid dysfunction
Primary hypothyroidism				
Tyrosine kinase inhibitors				
Imatinib, soraefanib, motesanib	Preexisting LT4 therapy: increase clearance of LT4	Increased LT4 requirement	<2 weeks	21%–100%
Sunitinib, dasatinib, nilotinib, axitinib, cediranib	Previously euthyroid patients: angiogenic activity	Hypothyroidism, occasionally preceded by mild thyrotoxicosis.	4–94 weeks	18%–85%
Immuno-therapies				
Interferon-α, Alemtuzumab, Ipilimumab	Stimulation of autoimmunity	Hashimoto thyroiditis	1–6 month	5%–50%
Immunomodulatory				
Thalidomide, Lenalidomide	T-cell stimulation, antiangiogenic activity, and induction of cytokine release	Ischemic or autoimmune thyroiditis	1–6 month Median: 5 months	7% 5%–10%
Secondary or central hypothyroidism				
Bexarotene				
	Decreased TSHB gene expression, reduced secretion of TSH	Central hypothyroidism	Hours-days	>90%
Immuno-therapies				
Ipilimumab, tremelimumab	Immune dysregulation with hypophysitis	Central hypothyroidism	9–24 week	5%–17%
Hyperthyroidism				
Immuno-therapies				
Ipilimumab, tremelimumab	Immune dysregulation	Graves' disease or painful thyroiditis	1–3 month	Rare
Alemtuzumab	Immune reconstitution abnormalities	Graves' disease or painful thyroiditis	6–31 month	10%–30%
Interferon-α	Immune reconstitution abnormalities	Graves' disease or painful thyroiditis	4–9 month	1%



Investigation

Thyroid function test revealed profound hypothyroidism with low fT4 at 7.2 pmol/L (reference range: 9.0–20.0 pmol/L) and an elevated TSH at 44.7 mIU/L.

Thyroid peroxidase antibody (TPO Ab) was positive – 405.8 IU/mL (reference range <5.6).

Thyroid ultrasound showed heterogeneous thyroid gland, which is suggestive of thyroiditis with no evidence of lymphadenopathy or suspicious nodules.

Treatment

Commenced on levothyroxine 50 µg daily, and dose was increased to 100 µg daily over four weeks.

Outcome and follow-up

Patient was reviewed recently in endocrinology outpatient department with a good clinical and biochemical response and recent thyroid function test was normal, a FT4 of 14.2 pmol/L and TSH 1.10 mIU/L.

Discussion

Pomalidomide is a third-generation immunomodulatory agent, a derivative of thalidomide, that is currently reserved for the treatment of patients with relapsed/refractory multiple myeloma. It works by inducing cell cycle arrest and apoptosis directly in multiple myeloma cells; enhances T-cell- and natural killer (NK) cell-mediated cytotoxicity; inhibits production of proinflammatory cytokines tumor necrosis factor- α (TNF- α), IL-1, IL-6 and IL-12 and inhibits angiogenesis (1). Neutropenia is the most common side effect of pomalidomide reported in up to 26–66% of patients treated while other common side effects includes anemia and thrombocytopenia (2). Fatigue, thromboembolic events, skin toxicities, hyperglycemia and peripheral neuropathies were considered to be the non-hematological adverse reactions of pomalidomide (3).

Thyroidal dysfunctions is a well-known side effect of certain antineoplastic agents through different mechanisms (Table 1) (4). Pomalidomide toxicities were studied previously but none mentioned any relation between hypothyroidism and pomalidomide (2). Hamadeh and coworkers described the first case of pomalidomide-induced hypothyroidism (2015) in a 51-year-old female, diagnosed with multiple myeloma, and she developed overt hypothyroidism after the fourth cycle

of pomalidomide (5). Unlike pomalidomide, thalidomide and lenalidomide may lead to hypothyroidism. Up to 20% of patients receiving thalidomide for multiple myeloma developed serum TSH greater than 5 IU/L, while 7% had a TSH greater than 10 IU/L (6). Additionally, up to 6% of patients with no previous history of thyroid dysfunction who received lenalidomide developed hypothyroidism in a retrospective study (7).

Pomalidomide have similar features of thalidomide (8). Several mechanisms have been suggested in the pathogenesis of thalidomide-induced hypothyroidism. These include inhibition of thyroid hormone secretion (9), reduction of iodine uptake into follicular thyroid cells (10) an anti-angiogenic effect disrupting the blood flow to the thyroid (6) and through an autoimmune thyroiditis process induced by deregulation of cytokine or direct effects of T-lymphocytes (6).

It is plausible that these mechanisms may be true for pomalidomide-induced hypothyroidism; however, further studies are needed to prove this relationship. Based on this case and others (5), we recommend measuring TSH before and then every 2–3 months while on pomalidomide as recommended (9).

In conclusion, overt hypothyroidism is a potential adverse effect of pomalidomide therapy. Practitioners prescribing this drug should be aware of this potential side effect and thyroid function test should be included as a screening test with regular review in patients receiving pomalidomide. Resumption of treatment with pomalidomide is not contraindicated once the hypothyroidism has been adequately treated.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent

Signed and verbal consent was obtained from the patient for the publication of this article.

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Received in final form 12 October 2017
Accepted 27 November 2017