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Case Report

Pomalidomide Induced Hypothyroidism in a Multiple Myeloma Patient: A Case Report

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Abstract

Pomalidomide is a third generation immunomodulatory agent that is currently reserved for the treatment of patients with relapsed/refractory multiple myeloma (MM). Unlike thalidomide and lenalidomide, hypothyroidism has not previously been reported as a side effect of pomalidomide. Herein, we report a case of hypothyroidism that acutely developed while the patient was receiving the 4th cycle of pomalidomide for refractory MM. The main manifestations were bilateral swelling of all extremities, muscle pain, and fatigue with serum creatinine up to 1.4 mg/dL. These clinical issues made us suspect hypothyroidism. Indeed, upon examination, her TSH was up to 173mIU/L. Her pomalidomide was stopped and she was started on replacement thyroid hormonal therapy with quick improvement in her symptoms and acute kidney failure. In conclusion, we report here the first case of pomalidomide induced clinically significant hypothyroidism. Thus, like with thalidomide and lenalidomide, practitioners prescribing pomalidomide should be aware of this complication and screen for it.

Keywords: Pomalidomide; Hypothyroidism; Immunomodulatory agents; Multiple myeloma

Case Presentation

Our patient is a 51 year old female with an unremarkable past medical history who was diagnosed with stage IIA IgG kappa MM back in December of 2007 when she presented with nonspecific complaints of fatigue and hot flashes. She was found to have microcytic anemia with a hemoglobin level of 9.9g/dL. Further work up including serum protein electrophoresis (SPEP) revealed an elevated serum total protein of 10g/dL (reference range: 6-8g/dL) and an M-spike of 4.8g/dL. Additionally, serum light chain assay showed the following: kappa light chain of 120mg/L (reference range: 3.3-19.4mg/L), lambda light chain of 4.1mg/L (reference range: 5.71-26.3mg/L), and a kappa to lambda ratio of 29.26 (reference range: 0.26-1.65mg/L). A skeletal survey revealed no lytic lesions, and a bone marrow biopsy indicated a hypocellular bone marrow with 70-80% plasma cells replacing the normal bone marrow cells. Her serum creatinine, calcium and albumin were all within the reference range. Finally, cytogenetic analysis revealed trisomy chromosome 5 and 7, and deletion of chromosome 13q.

The initial treatment consisted of liposomal doxorubicin (30mg/m^2) and weekly bortezomib 1.3mg/m^2. At this point in time, her thyroid stimulating hormone (TSH) and T3 levels were within reference range, 1.61mIU/L (reference range: 0.27-4.2mIU/L) and 131ng/dL (80-200 ng/dL), respectively. After receiving four cycles of the induction regimen, the patient underwent autologous peripheral blood stem cell transplant. Follow up studies revealed that she achieved partial remission of her disease. She did not receive post transplant maintenance. Two years later, her disease progressed as evidenced by a continuous or steady rise in her MM markers. Subsequently, she was treated with weekly SQ bortezomib 1.3mg/m^2, weekly dexamethasone 40mg, and lenalidomide 15mg D1-21 every 28 days. Dexamethasone was later omitted from the regimen because of insomnia and agitation. Her MM markers continued to improve with this regimen which she tolerated quite well without any complaints. After receiving 9 cycles, lenalidomide was discontinued and the patient was maintained on bortezomib 1.3 mg/m^2 SQ (4 weeks on and 2 weeks off). The patient received a total of 18 cycles of bortezomib maintenance with minimal peripheral neuropathy in her feet. However, following completion of cycle 18, the decision to discontinue bortezomib permanently was made since her MM markers were increasing. Eventually, the patient was switched to pomalidomide monotherapy, 2 mg orally for 21 days of each 28 day cycle. She initially responded, however four months into treatment, the patient complained of fatigue, intolerance to cold, weight gain and swelling in her hands and feet. In addition, her serum creatinine increased to 1.41mg/dL. In light of these complaints, pomalidomide was withheld. Further work up revealed a markedly elevated TSH level at 175mIU/L. Hence, the patient was diagnosed with mild myxedema and referred to an endocrinologist, and was subsequently started on levothyroxine (Synthroid®) 75 micrograms per day. Four weeks after discontinuing pomalidomide and initiating treatment with levothyroxine, her TSH level dropped considerably to 9mIU/L. At the same time, all her symptoms and renal failure improved back to her baseline. She is currently responding to treatment with oral cyclophosphamide and dexamethasone without any signs or symptoms of hypothyroidism.

Discussion

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal expansion of plasma cells in the bone marrow. With an estimated annual incidence rate of about 20,000 new cases, MM ranks second in terms of prevalence where it accounts for approximately 10% [1] of all cases of hematological malignancies (only second to Non-Hodgkin's lymphoma).

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Table 1: Antineoplastic agents associated with hypothyroidism.

Drug Class	Incidence	Proposed mechanism
BCR-ABL (TKI)* inhibitors:		
- Imatinib - Dasatinib - Nilotinib	90% 50% 22%	Nondeiodination clearance of T4, antiangiogenic activity
VEGF inhibitors		
- Sunitinib - Sorafenib - Axitinib - Pazopanib	53-85% 20-36% 83-92% 10-29%	Antiangiogenic activity
Immunotherapies		
- Interferon alpha - Alemtuzumab - Ipilimumab	< 5% 13-34% ≤ 2%	Autoimmune thyroiditis
Immunomodulators		
- Thalidomide - Lenalidomide	20% 5-10%	T-cell stimulation, antiangiogenic activity, and induction of cytokine release

*__Abbreviations__: TKI: Tyrosine Kinase Inhibitors; VEGF: Vascular Endothelial Growth Factor.

Although MM is an incurable disease, we have witnessed a dramatic improvement in patient survival over the past few decades [2] primarily attributable to a better understanding of the disease pathogenesis coupled with the emergence of novel agents targeting the aberrant pathways involved in its development. The current pharmacotherapies available for the treatment of MM can be broadly classified into five main categories: alkylating agents, steroids, proteasome inhibitors (PIs), immunomodulatory agents (IMiDs) and histone deacetylase inhibitors (HDACs). Pomalidomide, an oral third generation IMiDs, is the latest addition to the armamentarium of therapeutic options for patients with MM. It was granted accelerated FDA approval back in February of 2013 for use as monotherapy or in combination with dexamethasone in patients with relapsed/refractory MM. The approval came about following the encouraging findings from the CC-4047-MM-002 clinical study which recruited 221 patients with relapsed or refractory MM [3,4]. Of note, the CC-4047-MM-007 [5] study is evaluating the clinical efficacy of pomalidomide when added to bortezomib and low dose dexamethasone in previously treated multiple myeloma patients.

Given the fact that pomalidomide is a thalidomide derivative, the drug is potentially teratogenic, and thereby it is available through a restricted distribution program known as "POMALYST Risk Evaluation and Mitigation Strategy (REMS) Program" where only physicians certified with the program are eligible to prescribe it. Furthermore, pomalidomide is known to cause a variety of hematologic and non hematologic toxicities. To our knowledge, there are no prior reports of pomalidomide associated thyroid dysfunction in the medical literature. Herein, we describe the first case of hypothyroidism typified by a rapid clinical syndrome of hypothyroidism and elevation in TSH that, according to the time course and subsequent outcome, is most likely induced by treatment with pomalidomide.

Hypothyroidism is a well-known side effect of several antineoplastic drugs that belong to different pharmacologic classes (Table 1) [6-9]. Of note, drug induced hypothyroidism is sometimes overlooked given its nonspecific manifestations which tend to overlap with the other side effects of antineoplastic drugs and even with some of the manifestations of malignancies. Pomalidomide is the newest agent of the IMiDs family to gain FDA approval for the treatment of MM in the relapsed or refractory setting. Pomalidomide side effect profile encompasses hematologic (neutropenia, anemia and thrombocytopenia) as well as non hematologic toxicities of which fatigue, fever, skin rash, nausea, constipation, and peripheral neuropathy are the most common (i.e. reported in more than 10% of the patients treated with pomalidomide in phase III clinical trials) [3,10-12].

Pomalidomide and lenalidomide are structural derivatives of thalidomide, and both of these agents were developed for the sole purposes of improving the therapeutic efficacy of thalidomide and reducing its unwanted side effects. It is important to emphasize that hypothyroidism was not noted in any of the clinical studies that evaluated the efficacy of pomalidomide for refractory/relapsed multiple myeloma. Additionally, our literature search in PUBMED using the terms "pomalidomide" and "hypothyroidism" did not reveal any published case reports of pomalidomide induced hypothyroidism. Although renal injury was reported in < 5% in some clinical trials of pomalidomide, and a recent case report of crysral nephropathy from the use of poamlidomide and levofloxacin [13], the mild increase in creatinine seen in our case was felt to be related to the significant hypothyroidism with myxedema signs and symptoms. On the other hand, hypothyroidism has been associated with thalidomide [14,15] and lenalidomide [16,17] with a higher incidence seen with the former (20%) as opposed to 5-10% with lenalidomide. The time course of developing hypothyroidism was quite variable, ranging from 1 to 6 months. Although the exact mechanism of IMiDs induced hypothyroidism has not been fully elucidated yet, studies suggested that this side effect might be brought about by at least 4 potential contributing mechanisms [14,16-19]. These include direct toxic effect on the thyroid gland, inhibition of angiogenesis leading to ischemia and cell death, reduction in iodine uptake, and finally immune mediated destruction subsequent to stimulation of the T cells and altered endogenous cytokine release. Given the negative impact of drug induced hypothyroidism on the patient's quality of life which may result in therapy interruption, it is recommended that TSH levels be measured at baseline and regularly thereafter following

thalidomide or lenalidomide initiation [20] for early detection of impaired thyroid gland function which can be corrected by hormone replacement. While hypothyroidism was transient in some published case reports [16,21], the impairment described in one report was permanent, elicited by autoimmune destruction of the gland [17]. Pomalidomide possesses antiangiogenic activity as well as enhanced immunomodulatory effects [22-24] (co-stimulation of T cells and augmentation of NK cell activity) similar to its predecessors; both of which have been generally postulated as probable mechanisms of IMiDs induced hypothyroidism. With that said, the likelihood of pomalidomide induced hypothyroidism seems plausible.

The patient described here did not experience or complain of any symptoms suggestive of hypothyroidism while on lenalidomide or after. Moreover, the time elapsed from lenalidomide discontinuation to pomalidomide initiation was long enough (approximately 2 years) to offset any lenalidomide induced side effects including hypothyroidism, thereby lending further support that pomalidomide is most likely the culprit in this case. Finally, our patient developed hypothyroidism within 4 months of pomalidomide initiation which falls within the time frame documented with other IMiDs. Aside from pomalidomide, the patient's medication list throughout this whole period did not include any other medication known to cause hypothyroidism.

In conclusion, this report describes the first case of hypothyroidism caused by pomalidomide. Hence, it is central that health care providers be aware of this adverse effect and vigilant in screening for hypothyroidism routinely in MM patients receiving pomalidomide.

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