CASE REPORT

Hair repigmentation associated with thalidomide use for the treatment of multiple myeloma

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SUMMARY

A 75-year-old woman diagnosed with multiple myeloma in 2007 began treatment with monthly melphalan and prednisone for a total of 9 cycles in combination with thalidomide in 2009. The patient subsequently continued on thalidomide for long-term maintenance therapy. 3 years following initiation of thalidomide, the patient mentioned to her oncologist that her hair had become darker over the years. She attributed the change to thalidomide given the temporal relationship and progressive darkening over the course of therapy. The patient denies ever using any hair colouring treatments and had longstanding grey/white hair before beginning thalidomide in 2009. A case of hair repigmentation associated with the use of lenalidomide, a 4-amino-glutamyl analogue of thalidomide, in a patient with multiple myeloma was previously reported in the literature. We report herein the first case of hair repigmentation associated with the use of thalidomide, a related immunomodulatory drug.

BACKGROUND

Thalidomide is an immunomodulatory drug (IMiD) that is approved by Health Canada and the US Food and Drug Administration (FDA) for use in combination with melphalan and prednisone for the treatment of multiple myeloma. When added to melphalan and prednisone for the treatment of newly diagnosed multiple myeloma, thalidomide improves progression-free and overall survival.¹

First developed in 1956 as an oral sedative, thalidomide soon gained popularity in many countries as an antiemetic used in pregnancy until it was withdrawn from the market in 1961 due to severe teratogenic effects.² With more stringent guidelines in place surrounding its prescribing and dispensing, thalidomide re-emerged on the market decades later, first gaining FDA approval for management of the cutaneous manifestations of erythema nodosum leprosum in 1998, and then for the treatment of multiple myeloma in 2006.² While thalidomide has been associated with various adverse effects, including thromboembolism, myelosuppression, peripheral neuropathy, dizziness, somnolence, bradycardia, constipation and dermatological reactions such as mild-to-severe rash, dry skin, acne, alopecia and brittle nails, there have been no reports to date of changes in hair pigmentation related to thalidomide. However, a case of hair repigmentation associated with the use of lenalidomide, a 4-amino-glutamyl analogue of thalidomide, in a patient with multiple myeloma was recently reported.³ In their case report, Dasanu *et al*

hypothesised that lenalidomide, through its anti-inflammatory effects, may promote follicular melanogenesis through inhibition of cytokines involved in the negative regulation of melanogenesis. In addition, lenalidomide's endocrine effects on the hypophyseal-adrenal axis and its stimulation of migration/differentiation of melanocytes are also postulated mechanisms of hair repigmentation. We report herein the first case of hair repigmentation associated with the use of thalidomide.

CASE PRESENTATION

A 75-year-old woman was referred to the medical oncology clinic in 2007 for diffuse pain and multiple bony lesions. She had been diagnosed with monoclonal gammopathy of unknown significance in 1994 and had been stable until 2006, when she developed anaemia and marked osteopenia. Bone marrow biopsy revealed 10–15% plasma cells. The patient's medical history was significant for asthma, hypertension, migraines, hypothyroidism and breast cancer, which was diagnosed in 2003 and treated with mastectomy and chemotherapy (doxorubicin, cyclophosphamide and paclitaxel). Her medications at the time of presentation included anastrozole, diltiazem, indapamide, budesonide/formoterol turbuhaler, levothyroxine, ranitidine and multivitamins, all of which she had been taking for over 6 years. She is a non-smoker and a retired teacher who lives alone at home.

The patient began treatment with pamidronate for the bony lesions and epoetin alfa for anaemia in May 2007. Epoetin alfa was discontinued in August 2010 when the patient's haemoglobin was 117 g/L and has not been restarted since. She received pamidronate monthly until July 2009 when it was changed to an every 3 month regimen, which she continues to receive. In February 2009, the patient's paraprotein level increased to 56 g/L and treatment with monthly melphalan and prednisone (total of nine cycles) was initiated. Thalidomide 200 mg daily was added in April 2009 and continued until August 2010, at which point it was temporarily discontinued because the patient went into nearly complete remission, with a paraprotein level reaching as low as 2 g/L. In September 2010, thalidomide was restarted at the same dose due to a rise in paraprotein level. She continued to have good response to thalidomide, with the paraprotein level decreasing and becoming undetectable in April 2011.

During treatment, the patient developed some adverse effects attributable to thalidomide therapy. She experienced peripheral neuropathy

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(paraesthesiae of her fingers and toes) beginning in September 2009 and was eventually switched to a lower dose of thalidomide 100 mg every other day in July 2011. In July 2009, the patient experienced left thigh deep vein thrombosis (DVT), which was treated with dalteparin until 2012. The patient was not on any thromboprophylaxis prior to the DVT. Apart from these adverse effects, the patient did not experience any other known adverse effect related to thalidomide including somnolence, dizziness, constipation and bradycardia. In January 2012, the patient first mentioned to her oncologist that her hair had become darker over the years. She attributed the change to thalidomide given the temporal relationship and progressive darkening over the course of therapy. [Figure 1](#) shows the patient with greyish-white hair in July 2009, 3 months after starting thalidomide. Repigmentation of hair can be seen in [figure 2](#), which was taken in August 2014. The patient denies ever using any hair colouring treatments and had longstanding grey/white hair before beginning thalidomide in 2009. [Figure 3](#) provides a timeline of events from when the patient was diagnosed with multiple myeloma to when she first mentioned her hair repigmentation to her oncologist.

OUTCOME AND FOLLOW-UP

The patient continues to be on long-term maintenance therapy with thalidomide 100 mg every other day and receives pamidronate every 3 months. She remains in remission at age 84, and continues to have dark brown hair.

Figure 1 Photograph of the patient taken in July 2009, 3 months after starting thalidomide.

DISCUSSION

Hair repigmentation has been reported in various settings: as a postinflammatory event, postradiation therapy, following photosensitive dermatitis, in patients with celiac disease, etc.⁴ A number of drugs have also been implicated in causing hair repigmentation, although reports are not common and the mechanisms of repigmentation have not been fully elucidated. Follicular melanogenesis is coupled to the growth phase (anagen) of the hair cycle and has an extremely complex regulation system that involves hormones, neurotransmitters, cytokines, growth factors, eicosanoids and cyclic nucleotides.⁵ Stimulators of melanogenesis include α -melanocyte stimulating hormone, adrenocorticotrophic hormone, β -endorphin, prostaglandins, leukotrienes, endothelin (ET)1 and ET3, histamine, oestrogens, androgens, vitamin D₃ and bone morphogenetic proteins. Inhibitors of melanogenesis include melatonin, interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)- α , transforming growth factor (TGF)- β , interferon gamma, glucocorticoids, dopaminergic agonists and cholinergic agonists.⁵

This is the first case of hair repigmentation associated with the use of thalidomide, and the second case of hair repigmentation linked with the use of IMiDs. The mechanism of repigmentation is unknown. However, there are several hypotheses based on the numerous proposed mechanisms of IMiDs. Thalidomide's mechanism of action is complex and its molecular targets wide-ranging. It has antiangiogenic, proapoptotic, strong immunomodulatory and anti-inflammatory properties.⁶ For example, thalidomide's effect on TNF- α has been extensively studied and it has been shown to inhibit TNF- α synthesis, possibly by increasing the degradation of TNF- α mRNA or through inhibition of the gene transcription activator nuclear factor-kappa B (NF- κ B). Furthermore, in patients with myelodysplastic syndromes, treatment with thalidomide was found to decrease bone marrow TGF- β levels.⁷ In another study,

Figure 2 Photograph of the patient taken in August 2014 showing near-complete hair repigmentation after being on thalidomide therapy for 5 years.

Figure 3 Timeline of events from when the patient was diagnosed with multiple myeloma to when she first mentioned her hair repigmentation to her oncologist.

thalidomide treatment of cultured human lung fibroblasts resulted in decreased TGF- β and inhibition of TGF- β mRNA expression.⁸ Finally, animal models and in vitro studies with human tissue have also shown that thalidomide decreases the levels of IL-1 and IL-6. Thalidomide's inhibition of proinflammatory cytokines (TNF- α , TGF- β , IL-1 and IL-6), all negative regulators of melanogenesis, could explain in theory its effect on hair repigmentation, similar to the mechanism proposed by

Dasanu *et al*³ for lenalidomide.^{5 6} This hypothesis is supported by a recent case report wherein a 75-year-old woman with a 30 year history of uniformly grey-white hair experienced darkening of her hair 4 months after the initiation of adalimumab, a monoclonal IgG antibody against TNF- α , for the treatment of rheumatoid arthritis.⁹

There are no reports of hair repigmentation with any of the other medications that the patient was taking, with the

Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total Score:	3			

Figure 4 Naranjo adverse drug reaction probability scale.

exception of levothyroxine. Thyroid hormones have been shown to directly upregulate proliferation of hair matrix keratinocytes, prolong anagen duration and stimulate intrafollicular melanin synthesis in vitro on human anagen hair follicles.¹⁰ The authors postulate that the thyroid hormone may exert some of these effects through intrafollicular downregulation of TGF- β expression, as was also shown in vitro. There are few actual case reports of hair repigmentation associated with the thyroid hormone. A search of the literature found only a reference to two cases of grey hair repigmentation following treatment with high doses of tri-iodothyronine in an experimental study by Redondo *et al* that involved the application of tri-iodothyronine to hair follicles in in vivo and in vitro models.¹¹ Given that our patient had started levothyroxine and had been on a stable dose of 50 μ g daily for 8 years before any changes in hair pigmentation, it is unlikely that levothyroxine alone caused the repigmentation, although a synergistic effect between levothyroxine and thalidomide may be possible.

We report the first case in the literature of hair repigmentation associated thalidomide in a patient with multiple myeloma. As with the first case of hair repigmentation linked with an IMiD reported by Dasanu *et al*, it was the patient who, through curiosity and persistence, first noted gradual reversal of her greying hair and reported the change to her healthcare providers. In the previous case report by Dasanu *et al*, hair repigmentation was noticed as early as 6 weeks after starting lenalidomide. Although the patient in this case report did notice a gradual darkening of her hair over the years after starting thalidomide, the exact onset of repigmentation is unknown, making it more challenging to ascertain a strong temporal relationship between the drug and event. Nevertheless, the fact that the patient who had a longstanding history of grey/white hair prior to thalidomide now continues to have fully brown hair at age 84, 7 years after starting thalidomide, does lend support to the association. Application of the Naranjo algorithm for determining causality of adverse drug reactions resulted in a score of 3, indicating that the adverse drug reaction, hair repigmentation, is possibly caused by thalidomide (figure 4).¹²

While the mechanism through which IMiDs may cause hair repigmentation is unknown, the hypothesised mechanism of inhibiting proinflammatory cytokines involved in melanogenesis is certainly biologically plausible. Further understanding and observation of this reaction will provide insight into the ageing and melanogenesis processes, but will also help inform patients and clinicians about the incidence of this, perhaps a desirable, side effect of IMiDs.

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Contributors SL and WM contributed equally to drafting the manuscript. TB conceived of the project and helped write the manuscript. DA treated the patient, conceived the project and helped write the manuscript.

Learning points

- ▶ Hair repigmentation associated with medication therapy has previously been reported for a number of drugs, although the mechanisms of repigmentation have not been fully elucidated.
- ▶ Melanogenesis involves an extremely complex regulation system consisting of hormones, neurotransmitters, cytokines, growth factors, eicosanoids and cyclic nucleotides.
- ▶ This is the first reported case of hair repigmentation associated with thalidomide, and the second case linking hair repigmentation with use of an immunomodulatory drug. It is possible that thalidomide's inhibition of proinflammatory cytokines (TNF- α , TGF- β , IL-1 and IL-6), all negative regulators of melanogenesis, could explain in theory its effect on hair repigmentation.

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