Thalidomide for the Control of Severe Paraneoplastic Pruritus Associated With Hodgkin’s Disease

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Abstract
A 22-year-old woman with nodular sclerosis type II Hodgkin lymphoma diagnosed in June 2001. She initially underwent chemotherapy with 6 cycles of ABVD (adriamycin, bleomycin, vincristine, dacarbazine) regimen, leading to clinical remission. As it relapsed, she was again treated with 2 different chemotherapy regimens. In November 2003, she underwent bone marrow autotransplantation, but it relapsed after 2 months. After that, she was treated with chemotherapy in monotherapy until November 2005. In December 2005, she was referred to palliative care. Her main symptom was very severe pruritus that interfered with all aspects of her life, making her scratch continuously and interfering in all aspects of her life. She was treated with loratadine, hydroxyzine, prednisolone, paroxetine, mirtazapine, cimetidine, and ondansetron, individually and in various combinations. She also underwent ultraviolet phototherapy. All trials failed and her pruritus remained at level 8 of 10 most of the time. In April 2006, she started on thalidomide, 200 mg at night. The pruritus significantly improved to a level of 3 of 10 but did not disappear completely. She was at last able to sleep properly at night. She remained with a low level of pruritus until her death in July 2008, at the same dose of thalidomide.

Keywords
Hodgkin’s disease, palliative care, itch, thalidomide

Clinical Case
A 22-year-old woman with nodular sclerosis type II Hodgkin lymphoma diagnosed in June 2001. She initially underwent chemotherapy with 6 cycles of ABVD (adriamycin, bleomycin, vincristine, dacarbazine) regimen, leading to clinical remission. However, it soon relapsed and she was again treated with chemotherapy: the ESHAP (etoposide, solumedrol, high-dose ara-C, cisplatin) and MOPP (melphalan, oncovin, procarbazine, and prednisone) regimens. In November 2003, she underwent bone marrow autotransplantation, but it relapsed after 2 months. After that, she was treated with chemotherapy in monotherapy until November 2005. In December 2005, she was referred to palliative care. She was a young woman with a good performance status (ECOG 2). Her principal symptom was very severe pruritus that interfered with all aspects of her life, making her scratch continuously. She was unable to sleep properly due to pruritus. She would take more than 1 cold shower during the night to obtain transient relief from the pruritus. Her body was covered with lesions, many of them ulcerated. She was not jaundiced and blood tests of liver function were normal. A biopsy of a skin ulcer was compatible with scratching lesions.

She was treated with loratadine, hydroxyzine, prednisolone, paroxetine, mirtazapine, cimetidine, and ondansetron, individually and in various combinations. She also underwent ultraviolet phototherapy. All trials failed and her pruritus remained at level 8 of 10 most of the time. She was also being treated with morphine, sodium picosulphate, zolpidem, and diazepam.

In April 2006, she started on thalidomide, 200 mg at night. The pruritus significantly improved to a level of 3 of 10 but did not disappear completely. She was at last able to sleep properly at night. She remained with a low level of pruritus until her death in July 2008, at the same dose of thalidomide.

Discussion
Cutaneous manifestations of Hodgkin’s disease are common; most are nonspecific and can be present in over 50% of patients. The most well-recognized paraneoplastic finding is severe pruritus. Sometimes it is the presenting symptom of Hodgkin’s disease, but it is usually a sign of far advanced disease. Sometimes it persists after disease remission. In a
few cases the pruritus of Hodgkin’s disease is due to liver involvement and colestasis, but this patient was not jaundiced and the blood tests on liver function were normal.

Recommended treatment of pruritus related with Hodgkin’s disease includes palliative chemotherapy, corticosteroids, cimetidine, and mirtazapine. This patient underwent all these treatments and others without any benefit.

Thalidomide, a drug synthesized in 1954, was used extensively as a sedative, tranquilizer, and antiemetic. Thalidomide was the cause of multiple congenital abnormalities mainly concerning the limbs when used during gestation, sometimes after only a single dose. Because of these effects, it was withdrawn from markets at the beginning of the 1960s. Later on, the drug proved to be effective in the treatment of erythema nodosum leprosum. Nowadays, it is used for the treatment of many diseases and symptoms, namely in advanced cancer, such as anorexia. There are very rigid rules in women with reproductive potential to prevent its use during pregnancy.

The antipruritic activity of thalidomide can be secondary to the inhibition of tumor necrosis factor alpha. Another possibility is that its antipruritic effect results from its central depressive action. This nonspecific action seems more likely as thalidomide has proven to be effective in the relief of pruritus originating from very different causes. Besides teratogenicity, the major adverse effect of thalidomide is peripheral neuropathy. Other frequent adverse effects include rash, dizziness, constipation, tremor, mood changes, headache, and thromboembolism. This patient had none of those adverse effects. Thalidomide enhances the activity of alcohol, barbiturates, and chlorpromazine, and raises the serum levels of paracetamol, increasing its toxicity. Drugs that cause sedation or neuropathy should be used carefully, as well as drugs that decrease the efficacy of oral contraceptives.

Recently, Rubinstein and Duvic found that the pruritus of Hodgkin’s disease is commonly associated to Staphylococcus aureus colonization and that antibiotic therapy can significantly reduce the pruritus. We do not know whether this patient could have benefited from antibiotic therapy because this information was not available at the time and S aureus was not detected. Korfitis and Trafalis describe 4 patients, 3 with lymphoma and 1 with multiple myeloma, with intense generalized pruritus who improved with carbamazepine. Carbamazepine has previously been reported to alleviate pruritus associated to multiple sclerosis but not as far as I know in any other cases. Could carbamazepine have been a solution for this young woman?

Although, thalidomide has been described in several situations as an effective drug for pruritus, this is the first time that its effect was described in Hodgkin’s disease, as far as I know.

**Conclusion**

Pruritus may be a very distressing symptom. It is relatively frequent in Hodgkin disease and sometimes its control is very difficult as it was in this young woman. In such cases, thalidomide should be considered a potentially useful alternative.

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**References**