ification of the HSV IgM and IgG status of the patient would help in vindicating the new boyfriend.

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No potential conflict of interest relevant to this letter was reported.

1. Case Records of the Massachusetts General Hospital (Case 12-2013). N Engl J Med 2013;368:1537-45.

DOI: 10.1056/NEJMc1306332

**THE DISCUSSANT REPLIES:** Chandrasekar raises the possibility that the patient's dramatic pneumonic illness might have been the result of reactivation of HSV-1 rather than primary infection.

I initially evaluated this patient 3 days into her hospitalization and 3.5 weeks into her presenting illness. At that time, my working diagnosis was primary HSV pneumonia, and I recommended antibody testing for HSV IgM and IgG. The results from these tests were reported 8 days later, with the following results: the HSV-1 IgM level was less than 0.8 μg per milliliter (negative) and the HSV-1 IgG level was more than 5.0 μg per milliliter (positive). Unfortunately, the published case discussion did not include these specific antibody results.

The absence of virus-specific IgM and the presence of HSV-1 IgG provide support for the likelihood of reactivation of HSV-1. However, since the serologic tests were performed 1 full month into the patient's illness, there was also sufficient time for immunoglobulin-class switching to have occurred; this would have made primary infection a possibility. Nonetheless, probability favors reactivation.

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Since publication of his article, the author reports no further potential conflict of interest.

DOI: 10.1056/NEJMc1306332

# Reversal of Cushing's Syndrome by Vandetanib in Medullary Thyroid Carcinoma

**TO THE EDITOR:** Vandetanib was recently approved to treat symptomatic or progressive medullary thyroid cancer.[1] We report the effect of this drug in a patient with paraneoplastic Cushing's syndrome associated with medullary thyroid carcinoma.

A 58-year-old man was hospitalized for melancholic depression and difficulty walking due to muscle weakness. He had had debilitating diarrhea for several months. Left-sided medullary thyroid carcinoma associated with cervical and mediastinal lymph-node metastases was diagnosed. A tissue diagnosis was made with the use of a lymph-node biopsy specimen that showed positive calcitonin immunostaining. The plasma calcitonin level was 6900 ng per liter (2015 nmol per liter) (reference range, <10 ng per liter [<3 nmol per liter]) (Fig. 1A). Further tests revealed corticotropin-dependent Cushing's syndrome (morning serum cortisol level, 767 nmol per liter [reference range, 260 to 560] and adrenocorticotropic hormone level, 22 pmol per liter [reference range, <13]). The results of dynamic tests, which were concordant with an ectopic source of adrenocorticotropic hormone, showed a lack of a response to corticotropin-releasing hormone stimulation and a lack of cortisol suppression after administration of high-dose dexamethasone. No adenoma was seen on pituitary magnetic resonance imaging. Immunostaining of the tumor was positive for corticotropin. As described in nonpituitary tumors and in medullary thyroid carcinoma, an increase in the corticotropin level in response to desmopressin challenge tests was observed (Fig. 1B).[2]

Since Cushing's syndrome was the condition associated with the greatest risk for the patient, a sequential and combined cortisol-lowering therapy was initiated.[3,4] After several weeks of treatment with metyrapone and mitotane and a few weeks of treatment with somatostatin analogues and ketoconazole, the patient's symptoms and plasma cortisol level (Fig. 1A) remained unchanged. Mitotane and ketoconazole

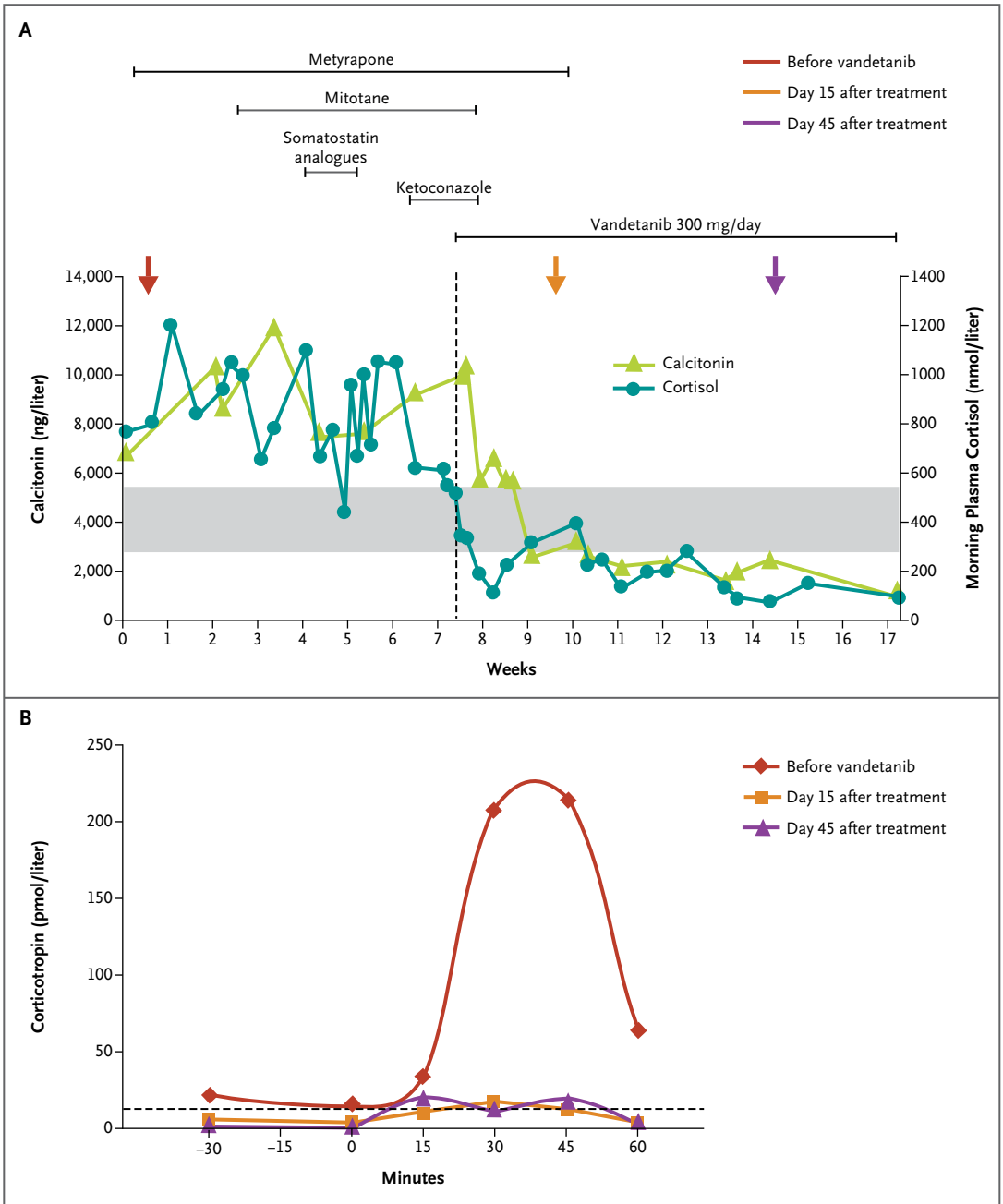


**Figure 1. Antisecretory Action of Vandetanib in a Patient with Paraneoplastic Cushing's Syndrome.**

Panel A shows changes in the calcitonin and cortisol levels in response to sequential and combined cortisol-lowering therapy followed by targeted therapy with vandetanib. The vertical dotted line denotes the initiation of vandetanib. The gray area corresponds to the normal range of morning plasma cortisol values (260 to 560 nmol per liter). The upper limit of the normal range for calcitonin is 10 ng per liter. The three arrows indicate the desmopressin challenge tests. Panel B shows corticotropin levels after desmopressin stimulation. Desmopressin was administered at 0 minutes. Basal levels of corticotropin correspond to –30 and 0 minutes. Corticotropin levels increased in response to desmopressin stimulation in the interval between 15 and 60 minutes. The dotted line represents the upper limit of the normal range for corticotropin (<13 pmol per liter).

were discontinued because of drug-induced neutropenia. At this stage, three options were considered: bilateral adrenalectomy, cervical and mediastinal surgery to reduce the tumor burden, and targeted therapy with vandetanib. The first two options were ruled out because of a deep-vein thrombosis necessitating anticoagulation; therefore, treatment with vandetanib was initiated. A rapid decrease in the cortisol level was observed (Fig. 1A). The simultaneous decrease in the calcitonin level and the blunted response of the corticotropin level to desmopressin after 15 days strongly suggested a direct antisecretory action on neoplastic cells (Fig. 1B). Computed tomography performed after 30 days did not reveal any reduction in the size of the mass. Cortisol-replacement therapy was initiated. The patient showed clinical improvement within the next weeks. A blunted response to desmopressin was again observed after 45 days (Fig. 1B).

This case shows a rapid antisecretory effect that was temporally dissociated from the antitumoral action; this effect has been described in vitro with a kinase inhibitor of the rearranged during transfection (*RET*) proto-oncogene.[5] Moreover, vandetanib may be a new therapeutic option in patients with paraneoplastic Cushing's syndrome and medullary thyroid carcinoma.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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DOI: 10.1056/NEJMc1301428

## Bellevue Drowning

Diesel fumes swirl, noxiously engulf sinuses,
mouth, lungs, brain;
Gasping for air, drowning in carbon monoxide,
Eyes burning, disoriented by a hurricane's
darkness,
Dizzy unsteady terrified stumbling for a door,
but

No relief, fumes throughout, joining black
flood waters below.
Hours before, a powerful gift, sparing certain
patients certain death —
Bellevue's life support in diesel form —
Now an enemy in unwelcome darkness.

Toxic fumes, mingling with sweat, urine,
stale air;
Fumes lingering for days in empty rooms,
A reminder of her near-death experience,
Bellevue's worst night, the night of my
nightmares.

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DOI:10.1056/NEJMc1301706