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**LETTER TO THE EDITOR**

# Behavioral disorders secondary to profound hypomagnesemia in a patient given cetuximab for metastatic colorectal cancer hypomagnesemia due to cetuximab treatment

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## To the Editor

A 66-year-old man was referred to our unit in May 2004 for treatment of a colonic adenocarcinoma located in the caecum with multiple hepatic and pulmonary synchronous metastases. A FOLFOX4 chemotherapy regimen [1] was initiated for this patient in good general health who was free of colonic symptoms. After six well-tolerated cycles, partial tumor response was noted and a stop-and-go strategy [2] was started. Chemotherapy was interrupted from August 2004 to January 2005 then reinstituted with the same protocol because of radiological progression. The patient presented severe anaphylactic reactions [3] during the first two new cycles so oxaliplatin was discontinued. There was no evidence of sensorial neuropathy. The patient then received six cycles of a FOLFIRI regimen through June 2005 and achieved tumor stabilization. After a second pause, tumor progression noted in September 2005 led to a third line of chemotherapy using FOLFIRI-cetuximab [4]. This regimen was well tolerated with the exception of moderate grade 1 acne-like rash [4]. The clinical situation improved and computed tomography demonstrated morphological stability after six cycles. Six complementary cycles were planned.

Before the ninth cycle, the patient's wife reported that the patient presented significant behavioral disorders for one week: irritability, fatigue, somnolence, confusion, temporospatial disorientation and falls. The patient was taking no medication between cycles. The neurological examination revealed grade 2/4 paresia of the lower right limb and paresthesia of the feet. The brain CTscan was normal. Blood chemistry revealed grade 3 (NCI-CTC) hypocalcemia (1.52 mmol/L; nl: 2.20–2.50 mmol/L; grade 4 <1.5 mmol/l); corrected calcemia was 1.73 mmol/L. Hypophosphoremia and hypomagnesemia were then suspected and confirmed: serum Ph: 0.51 mmol/L (nl: 0.80–1.60 mmol/L; grade 3), serum Mg: 0.43 mmol/L (nl:0.65–1.05 mmol/L; grade 3). Urine samples collected before corrective electrolyte infusions revealed renal wasting despite the very low serum levels: urinary Ph: 35.1 mmol/24h; urinary Mg: 4.2 mmol/24h; urinary Ca: 4.95 mmol/24h. Serum calcium measured at onset of cetuximab treatment was normal.

The neurological symptoms resolved after corrective intravenous infusion of calcium, phosphorus, and magnesium. Serum levels returned to normal with one week. The patient was discharged to his home with oral supplementation of magnesium and calcium. Chemotherapy was postponed a few weeks.

This adverse effect has been recently reported and explained by Schrag et al. [5] who described a clinical case with similar symptoms and blood chemistry. These authors retrospectively analyzed blood chemistry reports of 154 patients given cetuximab and discovered grade 3/4 hypocalcemia in 21% and grade 3/4 hypomagnesemia in 24% of the 34 patients tested (22%).

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The pathogenic mechanism of cetuximab-induced hypomagnesemia involves blockade of renal reuptake of free magnesium after glomerular filtration [6]. Normally, active reabsorption of magnesium ions in the distal convoluted tubule via TRPM6 clears urine of 70% of the filtered magnesium. TRPM6 binds to EGF receptors also present in the distal tubules. Cetuximab, blocks EGF receptors, and can thus inhibit magnesium reabsorption, provoking renal wasting of magnesium. Hypocalcemia and hypophosphatemia would be a secondary effect of low serum magnesium via peripheral blockade of parathormone.

We suggest that serum calcium, phosphorus and magnesium should be assayed in patients treated with cetuximab who develop a combination of peripheral and central neurological disorders associated with fatigue. The disorders generally resolve with correction of the hypomagnesemia. Regular (low-cost) monitoring of serum calcium and magnesium should be routine practice in patients treated with cetuximab.

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