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Letter to the Editor

Comment on "Elevation of Serum Carcinoembryonic Antigen Concentration Caused by Everolimus-Induced Lung Injury: A Case Report"

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We read with great interest the report of elevated serum carcinoembryonic antigen (CEA) following everolimus administration,[1)] in which it was reported that everolimus treatment for renal cell carcinoma with lung metastasis caused pulmonary ground-glass opacities accompanied by elevated serum CEA. Furthermore, interrupting everolimus resulted in improvements of both lung shadows and elevated CEA levels. As there have been no reports of correlations between everolimus and elevated CEA to date, the authors concluded that the elevated CEA could be caused by everolimus-induced lung injury.

CEA is one of the most widely used tumor markers, and serum CEA levels increase in gastrointestinal cancers, as well as other types of carcinomas. However, serum CEA also rises in non-neoplastic conditions, such as inflammatory diseases of the glandular epithelium, biliary obstruction, and metabolic disorders including hyperglycemia.[2)] Among these metabolic disorders, hypothyroidism is a frequent endocrinological disorder associated with elevated levels of certain tumor markers. It has been reported that a significantly high proportion of patients with Hashimoto's disease are CEA positive in the hypothyroid condition, and that hormone replacement therapy reduced CEA levels in these patients.[3)] Indeed, we recently experienced two non-neoplastic patients with severe hypothyroidism accompanied by drastically elevated CEA levels, which decreased with levothyroxine replacement therapy alone (**Table 1**). Although the precise mechanism for such deranged CEA elevation is not yet clear, it has been assumed that hypothyroidism affects CEA metabolism or hepatic clearance because CEA is metabolized and excreted by the liver.[3,4)] It is also well known that certain multi-kinase inhibitors, including sorafenib, which the authors administered just prior to everolimus, could induce thyroid dysfunction, especially in the Japanese population.[5,6)] Sorafenib can cause destructive thyroiditis followed by severe hypothyroidism, and even after discontinuing sorafenib, permanent or transient hypothyroidism can occur. From this point of view, we wondered whether hypothyroidism might have occurred after switching from sorafenib to everolimus, contributing, in part, to the elevated CEA.

However, as the authors mentioned, everolimus can cause some adverse metabolic events, including hyperglycemia and dyslipidemia, both of which are known to trigger elevated CEA levels.[2,7)] Oxidative stress and incrementally increased insulin-like growth factor (IGF)-1 levels due to hyperinsulinemia are assumed to be causes of CEA elevation.[8,9)] Based on these ideas, we would like to understand the clinical courses and changes in thyroid function and metabolic parameters before and after everolimus administration.

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Table 1 Relationship between thyroid function and serum carcinoembryonic antigen levels before and after levothyroxine treatment

Variable	Case 1		Case 2	
	Before	After	Before	After
Thyroid stimulating hormone (μU/mL)	146	2.68	170	1.39
Free T4 (ng/dL)	0.172	1.45	0.087	1.27
Carcinoembryonic antigen (ng/mL)	21.3	4.2	26.9	11.4

Molecularly targeted therapeutic agents are useful tools to treat unresectable advanced carcinomas; however, it is important to appropriately manage adverse endocrinological/metabolic effects. Additionally, we would like to advocate the importance of remembering that some metabolic and endocrinological disorders can increase the levels of certain tumor marker levels, such as unexplainably high serum CEA levels.

Disclosure Statement

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