Letters to the Editors

The association between tumor-infiltrating lymphocytes (TILs) and metastatic course in neuroendocrine neoplasms

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To the Editors:

We have read with interest the article by Crippa and colleagues[1] concerning the long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas, with particular emphasis on their morphology. Here, we report some of our histologic research on gastroenteropancreatic and lung neuroendocrine neoplasms, focused on tumor-infiltrating lymphocytes (TILs). We studied 25 surgical specimens (4 pancreas, 9 lung, 12 midgut) of well-differentiated (G1) neuroendocrine carcinoid tumors, according to the World Health Organization criteria,[1,2] all with a diameter >2 cm,[3] and confirmed by immunohistochemistry for chromogranin A, synaptophysin, and neuron-specific enolase.[3]

The following subtypes of lymphocytes were investigated: CD4 + T-helper, CD8 + T-cytotoxic, CD20+ B, and CD56+ Nk. Only the lymphocytes located within the tumor and not those in organized lymphatic centers have been considered TILs. We have categorized their presence as absent, mild, and moderate.[3,4]

A moderate lymphocytic infiltration was found in about 25% of these well-differentiated neoplasms, all of which had no distant metastases to liver or pulmonary hilar lymph nodes during a follow-up period >10 years; mild or absent lymphocytic infiltrates have been observed in those cases with metastatic spread, discovered synchronously or after follow-up of 10 years ($P < .05$). Our findings led us to support that a moderate lymphocytic infiltrate represents the local expression of an immunologic response to neoplastic cells, opposing their metastatic spread. Conversely, the absence of any substantial TILs may be a sign of an immunotolerance, likely secondary to tissue compatibility between host and neoplasia, or a local immunosuppressive action by tumor-specific molecular mechanisms. Both of these conditions can favor invasion of blood vessels or lymphatics and subsequent metastases.

Similarly, we have observed the absence of a similar lymphocytic immune response in small-cell lung cancers, which are histogenetically correlated with neuroendocrine carcinomas and have a great metastatic potential.[5]

The immunoscore should also be considered a further prognostic indicator,[6] able to identify those neuroendocrine neoplasms prone to metastasis and should also be taken into consideration among the morphology of pancreatic neuroendocrine carcinomas.

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References

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Commentary on: Post-thyroidectomy hypocalcemia is related to parathyroid dysfunction even in patients with normal parathyroid hormone concentrations early after surgery

To the Editors:

We read with interest the article "Post-thyroidectomy hypocalcemia is related to parathyroid dysfunction even in patients with normal parathyroid hormone concentrations early after surgery" by Raffaelli et al.[1] We congratulate the authors for researching a very important postsurgical complication after total thyroidectomy. After a thorough reading of the article, we have a few comments and questions.

Recently many authors have investigated the use of postoperative parathyroid hormone (PTH) estimation to predict postoperative hypocalcemia. Wiseman et al[2] developed an algorithm using postoperative parathyroid hormone levels (<10, 10–15, and >15 pg/mL) to reduce hypocalcemic complications of thyroidectomy.[2,3] In the present study by Raffaelli et al, 211/1,171 (18%) patients with euparathyroid (PTH >10