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One hundred and seven member family with the rearranged during transfection V804M proto-oncogene mutation presenting with simultaneous medullary and papillary thyroid carcinomas, rare primary hyperparathyroidism, and no pheochromocytomas: Is this a new syndrome–MEN 2C?

To the Editors:

We would like to thank Dr Bhargav for his interest in our paper and his good questions and observations. First, we would like to clarify our protocol. The majority of the family members that we discussed were diagnosed within 2 years prior to submission of this report.[1] All patients were followed by an endocrinologist or endocrine surgeon and were tested with calcitonin assay at the time of their first evaluation along with RET testing.

Four branches of this family are being followed by 1 of our co-authors, a medical adult endocrinologist. Several members of the third generation are being followed by a pediatric endocrinologist. All adult RET mutation carriers were advised to have a total thyroidectomy. This recommendation was also conveyed to children 5 years of age and older.[2] Some family members considering total thyroidectomy remain undecided and continue to be followed for the presence of disease with assessment for thyroid nodules and serum calcitonin levels. The motivation for publishing data from this family was to bring attention to the presentation of the syndrome as the result of this specific mutation and to consider earlier prophylactic thyroidectomy.

The carriers of the RET V804M proto-oncogene mutation who rejected prophylactic thyroidectomy were observed with the following protocol: patients who had no clinical evidence of the disease (normal calcitonin level, normal thyroid ultrasonography) were followed with blood calcitonin levels every 3 months for the first year and then every 6 months. Thyroid ultrasonography was performed every 6 months for the first year and then once a year.[2,3]

With any suspicious findings, a more extensive workup was performed. For example, a member of the third generation with normal blood calcitonin level and normal thyroid ultrasonogram on initial presentation was then followed with another neck ultrasonography. An enlarged neck lymph node was biopsied and appeared to be a benign inflammatory lymph node. In our facilities, RET positive, asymptomatic patients were evaluated annually for primary hyperparathyroidism and pheochromocytoma and we found none.[2]

The follow-up protocol after the operation was similar to the protocol for initial evaluation of the asymptomatic patients, with exclusion of those patients with persistently detectable calcitonin levels.[2,3] For example, a first generation family member with extensive metastatic medullary thyroid carcinoma (MTC) at initial presentation had a total thyroidectomy and modified radical neck dissection and then had persistent, mildly increased but stable, calcitonin levels below 100 mg/dL. This patient was evaluated every 3 months over the last 2 years since primary operation. Calcitonin levels have remained unchanged without clinical evidence of disease on ultrasonography or other imaging studies (positron emission tomography/computed tomography). The stable presentation, advanced patient age, and potential risks of reoperation in this case outweigh possible benefits of re-exploration.[3] Due to the short follow-up, we do not have information of any recurrences in the other family members.

We completely agree with Dr Bhargav's comments on the phenomenon of genetic anticipation in this family, and we plan to investigate it further.

We continue studies to rule out other possible explanations for the increased incidence of papillary thyroid carcinoma (PTC) in this family. Findings of PTC in RET carriers were described previously by Brauckhoff et al.[4] He reported that 9.1% of patients with RET mutations in exons 13 and 14 who were operated were found to have PTC. Specifically, he described a 24-year-old female with RET V804M mutation who was found to have a 2-mm PTC but no C-cell hyperplasia (CCH). Several other papers describe PTC in RET V804M mutation carriers simultaneously with CCH or MTC. Feldman et al in 2000 presented 2 families with the RET V804M mutation where 5 members were found to have simultaneous PTC and MTC/CCH.[5] Papi et al in 2003[6] and Foppiani et al in 2008[7] reported similar cases. If PTC is found to be a result of this familial RET V804M mutation and/or other genetic factors, we do hope this would be considered when making decisions for earlier thyroidectomy.

We thank Dr Bhargav for bringing to our attention the paper by Vriens et al,[8] an excellent review of our current knowledge of hereditary nonmedullary thyroid cancer. Several candidate genes have been identified that may contribute to these cancers. We support the idea of establishing a registry that would be used to illustrate the distinct phenotypic features associated with specific gene mutations. Ultimately, this knowledge will help the clinician and lead to improved outcomes for patients and their families.

Alexander L. Shifrin, MD, FACS[a]
Angela M. Fay, MS, CGC[b]
Cristina Z. Xenachis, MD[c]
Jerome J. Vernick, MD, FACS[a]
[a]*Department of Surgery*
[b]*Department of Oncology,*
Jersey Shore University Medical Center
Neptune
[c]*Downtown Osteoporosis Center*
Matawan, NJ
E-mail: ashifrin@meridianhealth.com

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