The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 49, Sep. 2025
ISSN No. 2078-2101



The Official Journal of the Gulf Federation For Cancer Control

Table of Contents

Original Articles

Survival Outcomes of Penile Cancer Patients undergoing Primary Surgery: Experience from a Tertiary Cancer Care Centre in South India **07**
Ricky Koshy Benjamin, Sivaranjith J, Madhu Muralee, Aswin Kumar, Jagathnath Krishna K. M

Incidental Radiation Exposure to the Internal Mammary Lymph Nodes in Breast Cancer Patients Undergoing Intensity–Modulated Radiation Therapy: A Retrospective Analysis **16**
Vishwadeep Mishra, Shashank Shekhar, Sudeep Bisht, Rachita Chatterjee, Laxman Pandey, Archana Pandey

Safety and Outcome Analysis of Preoperative chemoradiation in Esophageal carcinoma **22**
Shuchita Pathak, Santhosh KD, Parikshith J, Rasmi Palassery, Vinayak V Maka

Impact of size of ovoids with Intra–cavitary Brachytherapy on dose to point A in patients with Cancer Cervix **28**
Dr. Tanvir Pasha, Dr. Nikhila Radhakrishna, Dr. Rekha Reddy Buchapudi, Dr. Saritha Sunny Pullan, Dr. Hamsini R S, Dr. Elna Jerod, Dr. Naveen Thimmaiah, Dr. Sridhar Poojar, Dr. Uday Krishna, Dr. Siddanna Rudrappa Palled, Dr. Thejaswini B, Dr. Lokesh Viswanath

De novo mutation of the RET proto–oncogene revealing multiple endocrine neoplasia type 2A: a sporadic case from Western Algeria **35**
Amina Chami, Pauline Romanet, Fatima Mohammedi, Nadia Benabadji, Narimane Habour, Dalia Derkaoui, Tewfik Sahraoui

Predictors of Recurrence and Long–Term Outcomes of Intracranial Meningiomas: A Retrospective Multicenter Study from Saudi Arabia **40**
Afnan Alkhotani, Rothaina Saeedi, Haneen Alomar, Fahad Alghamdi, Joudah Almaghrabi, Mohammed Binmahfoodh, Saleh Baeesa

Quality of Life (QoL) using EORTC QoL–C30 and BN20 among Patients who Underwent Brain Tumor Resection in a Tertiary Care Center in Saudi Arabia **53**
Rana H. Moshref, Leena H. Moshref, Fatemah A. Alhalawani, Masaheer A. Aljehani, Noor M. Shibriq, Wafa A. Saber, Ahlam B. Khojah, Rawan M. Alsayed, Razan Daghistani , Khalid M. Bajunaid, Mohammed A. Alyousef, Abdulrahman J. Sabbagh, Saleh S. Baeesa

Is there a Correlation between estrogen receptor expression level and early breast cancer survival? A Retrospective Study **65**
Ayman Rasmy, Ahmed Zeeneldin , Walid Abozeed, Saeed Al–Ghamdi and Shereef Elsamany

Efficacy and Safety of Paclitaxel Plus Ramucirumab as Second–Line Therapy in Advanced Gastric Cancer: A Retro–Prospective Single–Centre Study **75**
Varun Goel, Arpit Jain, Nivedita Patnaik, Dharmistha Basu, Shaifali Goel, Akanksha Jaju, Vineet Talwar, Shivendra Singh

Single Centre Experience of Treating Children with Cancer in the United Arab Emirates **80**
Mehnaz Aabideen, Arya Ashokan, Dr.Sagar Mohan Nivargi, Dr. Mohammed Ramzan, Dr. Deepthi Boddu, Dr. Fouzia Aboobacker, Abdullah Odat, Mohammed Taher, Dr. Rawia Mohamed, Dr. Rajasekhar Cingapagu, Prof. Dr. Humaid O. Al Shamsi, Dr. Zainul Aabideen

Review Articles:

Histopathological and Molecular Features of the Mammary Sclerosing Adenosis Lesions and Their association with breast carcinoma: Review of literature **85**
Rabab Ahmed Mohammed, Amina Ismaeel, Fayek Al Hilli

Conference Highlights/Scientific Contributions

- **News Notes** **93**
- **Advertisements** **96**
- **Scientific Activities** **97**

Original Article

De novo mutation of the *RET* proto–oncogene revealing multiple endocrine neoplasia type 2A: a sporadic case from Western Algeria

Amina Chami[1], Pauline Romanet[2], Fatima Mohammedi[3], Nadia Benabadji[3], Narimane Habour[1], Dalia Derkaoui[1], Tewfik Sahraoui[1].

[1]Lab. Bio. Dev. Diff. Université Oran 1 Ahmed Ben Bella, Faculté des Sciences de la Nature et de la Vie, Département de Biologie, Oran, Algérie.
[2] Laboratoire de Biologie Moléculaire, Biogénopole Timone, Marseille
[3] Clinique d'endocrinologie et diabétologie, CHU Oran, Algérie

Abstract

Background: Multiple endocrine neoplasia type 2A (MEN2A) is a rare autosomal dominant disorder associated with RET proto–oncogene mutations. Early diagnosis is absolutely critical for managing and preventing aggressive forms of medullary thyroid carcinoma (MTC) and associated tumours. Our aims are to confirm the clinical diagnosis and to detect, in relatives, those who bear the familial mutation in order to benefit from medical management before the first symptoms appear. Case Presentation: We report a sporadic case of MEN2A in a 34–year–old woman from western Algeria. She presented with bilateral medullary thyroid carcinoma and a left pheochromocytoma. Results: Genetic analysis by next–generation sequencing revealed a de novo heterozygous c.1901G>C (p.Cys634Ser) mutation in exon 11 of the RET gene. This is a well–known pathogenic variant associated with MEN2A. Discussion: This case proves that RET genetic testing is vital in all cases of MTC, even in those without a family history, as de novo mutations can occur. The absence of this variant in the patient's first–degree relatives confirms the de novo origin, possibly linked to advanced paternal age. Conclusion: Systematic genetic screening and counselling are essential for the early diagnosis and appropriate management of MEN2A, particularly in sporadic cases. Broader implementation of molecular testing and genetic counselling in Algeria is recommended to improve patient outcomes and prevent transmission to future generations.

Keywords: MEN2, RET, De Novo Mutation

Introduction

Medullary thyroid carcinoma (MTC) is a tumor arising from the parafollicular cells, or C cells, of the thyroid gland. MTC is sporadic in 75% of cases and familial in 25% [(1–3)], mainly due to multiple endocrine neoplasia type 2 (MEN2). MEN2 is an autosomal dominant genetic syndrome principally characterized by the association of medullary thyroid carcinoma (MTC) with other endocrine tumours. The prevalence of MEN2 is approximately 1/35,000. The penetrance of MEN2 is very high and the expressivity is variable. MEN2 is classified into three clinical subtypes [(1)]: i) MEN2A (OMIM#: 171400) is defined by MTC associated with pheochromocytoma and/or primary hyperparathyroidism (PHPT); ii) MEN2B (OMIM#: 162300) is defined as early and aggressive form of MTC in association with pheochromocytoma but without PHPT, and iii) in familial medullary thyroid carcinoma (FMTC, OMIM#: 155240), MTC is the only clinical manifestation of the disease [(2)]. MEN2A accounts for 95% of MEN2 cases. MEN2 can affect all age groups, with manifestations beginning in infancy to early childhood (MEN2B) or adulthood (MEN2A). MTC affects all forms of MEN2 and is the first manifestation of the disease. In MEN2A, MTC is definitively associated with pheochromocytoma (PCC) in 50% of cases and with PHPT in 20–30%. PCC is almost always benign and is usually multicentric, bilateral, and confined to the adrenal gland. In classical MEN2A, PHPT is usually mild and between one to four parathyroid glands may be enlarged. MEN2A can also be associated with

Corresponding author: Amina CHAMI BOULÉNOUAR, Lab. Bio. Dev. Diff. Université Oran 1 Ahmed Ben Bella, Faculté des Sciences de la Nature et de la Vie, Département de Biologie, Oran, Algérie.
E–mail: chami.amina@univ–oran.dz/ aminachami2023@gmail.com

cutaneous lichen amyloidosis or Hirschsprung's disease (HD, OMIM#: 142623).

MEN2 is caused by a heterozygous germline activating mutation in the *RET* proto–oncogene (10q11.2), encoding a membrane tyrosine kinase receptor. The clinical subtypes depend on which functional domain the mutations affect. 95% of patients with MEN2A have *RET* germline mutations in codons 609, 611, 618, or 620 of exon 10 or codon 634 of exon 11[4].

Approximately 95% of patients with MEN2B, *RET* germline mutations occur in exon 16 (codon M918T) and fewer than 5% have *RET* germline mutations in exon 15 (codon A883F) [5–8]. Almost all published reports on MEN2B concern patients with the *RET* codon M918T mutation and little is known about the clinical behaviour of patients with the *RET* codon A883F mutation. Recent reports, however, suggest that patients with the A883F codon mutation have a less aggressive MTC compared to patients with the M918T codon mutation [9]

Each of these syndromes is associated with specific mutations of the *RET* proto–oncogene [10, 11]. This good genotype–phenotype correlation allowed to stratify *RET* proto–oncogene mutation carriers into risk levels of developing aggressive CMT according to the American Thyroid Association (ATA). A first classification was proposed in 2009 and was revised in 2015[12]. The tool includes three increasing levels of risk: moderate, high and very high. This allows us to evaluate the individual risk more precisely and to propose recommendations on the age of the genetic study in relatives. It also allows the optimal age for prophylactic thyroidectomy to be estimated (Table I).

To date, very few reports have been published about the spectrum of *RET* proto–oncogene mutations in Algeria [13, 14]. This study from western Algeria is presented to illustrate a suspected MEN2A case whose genetic diagnosis revealed a mutation of the *RET* gene.

Patient and Methods

Our 34–year–old patient is being followed up in the endocrinology department of the Laribère Clinic in Oran, Algeria. Clinically, this patient presents the characteristics of a form of sporadic MTC: early age of onset <35 years, bilateral involvement [MTC of the left thyroid and a right thyroid nodule (poorly differentiated carcinoma)]. This patient also has a left PCC and has undergone an adrenalectomy. Data on the occurrence of tumours, clinical characteristics **(Table II)** and pedigree data were collected **(Figure 1)**. The patient agreed to the protocol of this study and provided written informed consent. Ethical approval was obtained from appropriate institution.

Mutation analysis

Peripheral blood collected on EDTA was obtained from the index case. Genomic DNA was extracted with QiaSymphony DS DNA Midi Kit (Qiagen, Courtaboeuf, France) from blood lymphocytes. *RET* (NM_020975) was sequenced by next–generation sequencing (NGS) with a minimum depth of 30X on Nextseq1000 sequencer (Illumina) after targeted amplification of all coding regions and intron–exon junctions of the 5,8, 10, 11, 13, 14 15, 16 exons, using a panel custom kit (CDHS_38758Z_1325 Qiagen) according to the manufacturer's instructions. The alignment, variant calling and annotations were performed using the CLC Genomics Workbench (Qiagen) and based on human genome GRCh37/hg19.

Risk of aggressive CMT	Codon	Age of genetic test for relatives
Moderate	533 609 611 618 620 630 631 768 790 804 891 912	< 3–5 years
High	634 et 883	<3 years
Very high	918 Patients with NEM2B	as soon as possible <1 ans

Table 1: Age of genetic study in relatives according to the mutation of the *RET* proto–oncogene.
Adapted from: Medullary thyroid cancer: management guidelines of the American Thyroid Association [12]

Id–patient	Age at first diagnosis	Thyrocalcitonin levels	PTH levels	Family History	Personal History
BR–34	31 ans	585.2 pg/ml	30.2 pg/ml	No first–degree relatives are also affected No family history of CMT	Loco Regional recurrence of MTC Personal history of left PCC

Table 2: Clinical characteristics and family history of MEN2 family

Results

The well–known activating *RET* pathogenic variant c.1901G>C , p. Cys634Ser was identified in the index case [12]. This missense variant is located in the exon 11 (Figure1), it causes an amino acid change Cysteine versus Serine that is classically involved in MEN2A.

Discussion and Conclusion

The codon Cys634 is located in a cysteine–rich domain close to the cell membrane. The presence of point mutations in one of the five highly conserved cysteine residues in the extracellular part of the *RET* proto–oncogene located close to the transmembrane domain causes MEN2A or FMTC [10, 11, 15]. Biochemical analysis of the c–RET protein with MEN2A mutation demonstrated that it is activated by ligand–independent homodimerization of the c–RET protein on the cell surface, leading to activation of its intrinsic tyrosine kinase. Amino acid sequencing revealed that 27 of 28 cysteine residues in the extracellular domain are conserved in the human and mouse c–RET proteins, suggesting that most of these cysteine residues could be involved in the formation of intrachain disulfide bonds that are crucial for appropriate tertiary structure of the c–RET protein. As a result of the MEN2A mutations in which one cysteine residue is lost, it is possible that another cysteine is unpaired and involved in the formation of aberrant intra– or intermolecular disulfide bonds in the mutant protein. This will cause the unpaired cysteine of a RET monomer to automatically pair with a cysteine opposite another RET monomer. These conformational changes followed by receptor dimerization will result in activation of the Tyrosine Kinase domain [15–17]. MEN2A mutations confer a dominant transforming potential to the mutated *RET* allele and represent gain–of–function mutations. Although activation of the c–RET protein by MEN2A mutations is reminiscent of that of these genes, this type of mutation of the c–RET protein might represent the first example for the mechanism of the development of human neoplastic disease. According to the American Thyroid Association MTC, this variant is associated with a high risk of aggressive MTC (Table1) and a risk of pheochromocytoma in 50% of cases and primary hyperparathyroidism in 20 to 30% of cases [12,19].

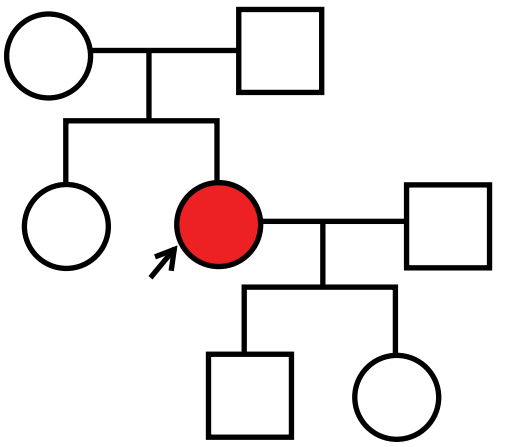


Figure 1: Pedigree of the reported patient (BR–34)

In this study, NGS sequencing analysis revealed a pathogenic variant of the *RET* gene. This is a well–known pathogenic variant in the literature [12]. Our patient has

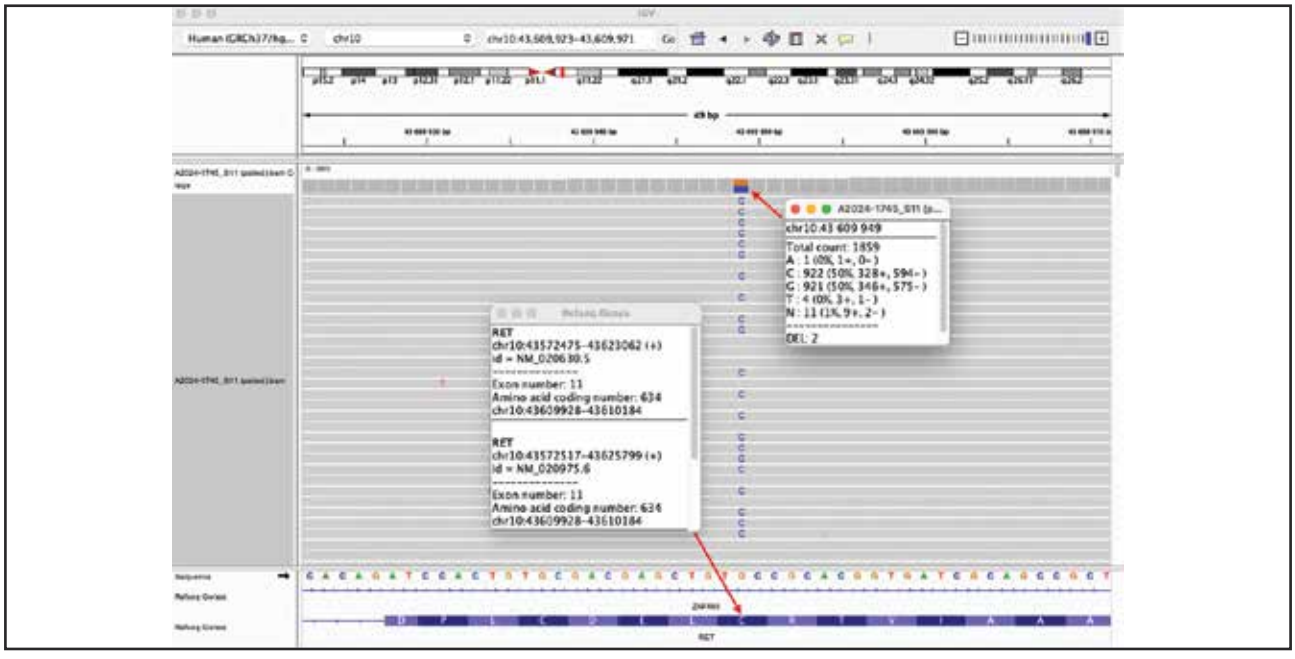


Figure 2: Integrative Genomics Viewer images of NGS analysis of the RET gene (forward sequence) for index case. The arrow indicates the variant nucleotide. The reference sequence is presented at the bottom of Fig. 2

multiple endocrine neoplasia type 2A and should receive appropriate management, knowing that this variant is associated with a high risk of aggressive CMT and a risk of primary hyperparathyroidism in 20 to 30% of cases. Our patient's family history does not reveal any cases of CMT. First–degree relatives were also checked, and the mutation was not found, confirming that it is de novo. The literature clearly shows that de novo mutations are favoured by an advanced paternal age, which we found in our patient's father who was 70 years old. The disease is autosomal dominant with a risk of transmission to offspring of 50%. Genetic counseling should be offered to this patient and her descendants. It is imperative that the genetic study in descendants is conducted without delay and before the age of three years[12, 18, and 19]. Our study highlights the importance of the molecular study of *RET* for the management and monitoring of patients with MEN2, in particular to differentiate the MEN2A and MEN2B subtypes and predict the risk of aggressive MTC. The systematic molecular study of the *RET* gene in front of any MTC allows the diagnosis of hereditary forms and a study of relatives genetically at risk. The epidemiological study should be initiated in order to list all MEN2 families on the national territory.

Furthermore, in order to optimize the diagnosis and management of these pathologies in our country, we recommend the integration of systematic genetic tests for the early diagnosis of monogenic diseases, which allows identifying patients at risk, avoiding inappropriate treatments, and proposing prevention strategies. It is essential to involve genetic counsellors in the management process. These professionals specialized in the interpretation of genetic test results and in patient support, can play a crucial role in providing clear information on genetic risk, treatment options, and implications for the family.

To ensure a better understanding of the mechanisms underlying monogenic diseases, the intervention of molecular biologists is essential. These experts play a central role in the analysis of genetic data and the improvement of personalized treatments based on the molecular profile of the disease. The objective of these recommendations is to enhance the care pathway for patients with monogenic hereditary diseases. This will be achieved by facilitating faster and more accurate diagnosis, more effective therapeutic decision–making and appropriate family management.

Acknowledgement

I would like to thank the endocrinopathy and genetics training team at the University of Aix–Marseille for the high quality of the programme and the endocrinology clinic for their warm welcome. I would also like to thank the patients for their participation and Professor Nidhal Chami for reviewing the manuscript.

Funding and Conflict of Interest

The author declares no conflict of interest in relation to this article

References

1. Santoro M, Carlomagno F, Romano A, et al. Germline mutations of MEN2A and MEN2B activate *RET* as a dominant trasforming gene by different molecular mechanisms. Science 1995 ; 267: 381–383.
2. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001; 86:5658–5671.
3. Schimke RN. Genetic aspects of multiple endocrine neoplasia. Annu Rev Med 1994; 35:25–31.
4. Raue F, Frank–Raue K 2012 Genotype–phenotype correlation in multiple endocrine neoplasia type 2. Clinics (Sao Paulo) 67(Suppl 1):69–75.
5. Carlson KM, Dou S, Chi D, et al. Single missense mutation in the tyrosine kinase catalytic domain of the *RET* proto–oncogene is associated with multiple endocrine neoplasia type 2B. Proc Natl Acad Sci U S A 1994; 91:1579–1583.
6. Eng C, Smith DP, Mulligan LM, et al. Point mutation within the tyrosine kinase domain of the *RET* proto–oncogene in multiple endocrine neoplasia type 2B and related sporadic tumours. Hum Mol Genet 1994; 3:237–241.
7. Smith DP, Houghton C, Ponder BA. Germline mutation of *RET* codon 883 in two cases of de novo MEN2B. Oncogene 1997; 15:1213–1217.
8. Gimm O, Marsh DJ, Andrew SD, et al. Germline dinucleotide mutation in codon 883 of the *RET* proto–oncogene in multiple endocrine neoplasia type 2B without codon 918 mutation. J Clin Endocrinol Metab 1997; 82:3902–3904.
9. Jasim S, Ying AK, Waguespack SG, et al. Multiple endocrine neoplasia type 2B with a *RET* proto–oncogeneA883F mutation displays a more indolent form of medullary thyroid carcinoma compared with a *RET* M918T mutation. Thyroid 2011; 21:189–192.
10. Mulligan LM, Kwok JBJ, Healey CS, et al. Germ–line mutations of the *RET* proto–oncogene in multiple endocrine neoplasia type 2A. Nature 1993: 363: 458–460.
11. Mulligan LM, Eng C, Healey CS, et al. Specific mutations of the R€T proto–oncogene are related to disease phenotype in MEN 2A and FMTC. Nature Genet 199 : 46: 70–74.
12. **Wells SA Jr,** Asa SL, Dralle H, et al. American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015 ; 25:567–610.

13. Chikouche A. Néoplasie endocrinienne multiple de type 2A associée à une mutation de novo du proto–oncogène PET. Batna J Med Sci 2015;2:117–120.

14. Chikouche, A, Ould Bessi, N, & Habak, N. Analyse moléculaire d'une famille algérienne de NEM2A au CPMC, Alger. Batna Journal of Medical Sciences 2020; 7(2), 197–200.

15. Donis–Keller H, Dou S, Chi D, et al. Mutations in the *RET* proto–oncogene are associated with MEN 2A and FMTC. Hum Mol Genet 1993; 2:851–856.

16. Asai N, Iwashita T, Matsuyama M, Takahashi M. Mechanism of activation of the *RET* proto–oncogene by multiple endocrine neoplasia 2A mutations. Mol Cell Biol. 1995 ; 15(3):1613–9.

17. Maruyama ST, Iwashita T, Imai H, et al. Germline mutations of the *RET* proto–oncogene in Japanese patients with multiple endocrine neoplasia type 2A and type 2B. Jpn. J. Cancer Res 1994; 85:879–882.

18. Rohmer V, Vidal–Trecan G, Bourdelot A, et al. Groupe Français des Tumeurs Endocrines. Prognostic factors of disease–free survival after thyroidectomy in 170 young patients with a *RET* germline mutation: a multicenter study of the Groupe Francais d'Etude des Tumeurs Endocrines. J Clin Endocrinol Metab. 2011; 96(3):E509–18.

19. Wells SA Jr, Pacini F, Robinson BG, Santoro M. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. J Clin Endocrinol Metab. 2013; 98(8):3149–64.