Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Case Report

Comprehensive management of multiple endocrine neoplasia Type 2A (MEN2A): A multidisciplinary approach

Neelima Gupta[1], Nimisha Srivastava[1], Jyoti Verma[2*], Pranjal Srivastava[3]

[1]Dept. of Pathology, Maharani Lakshmi Bai Medical College, Jhansi, Uttar Pradesh, India
[2]Dept. of Pathology, All India Institute of Medical Sciences, Mangalagiri, Guntur, Andhra Pradesh, India
[3]Dept. of Radiodiagnosis, Command Hospital, Lucknow, Uttar Pradesh, India

Abstract

Background: Multiple Endocrine Neoplasia Type 2A (MEN2A) is an autosomal dominant disorder characterized by medullary thyroid carcinoma (MTC), pheochromocytomas, and hyperparathyroidism. Early identification through genetic testing for RET proto-oncogene mutations and appropriate surgical interventions, such as prophylactic thyroidectomy, are crucial for optimal patient outcomes.

Case Description: A 42-year-old male presented with episodic hypertension and palpitations. Imaging studies, including computed tomography (CT) and ultrasound, revealed bilateral adrenal masses and thyroid nodules. Genetic analysis identified a mutation in the RET proto-oncogene, confirming a diagnosis of MEN2A. The patient underwent bilateral adrenalectomy and total thyroidectomy. Histopathological examination confirmed bilateral pheochromocytomas and MTC. Postoperative management included monitoring for hyperparathyroidism, a component of MEN2A, through regular assessments of serum calcium and parathyroid hormone levels.

Conclusion: This case underscores the importance of comprehensive evaluation in patients with endocrine tumours, including genetic testing for MEN2A. Early diagnosis and tailored surgical management are vital to prevent complications associated with this syndrome. Recognizing the constellation of symptoms associated with MEN2A allows for timely intervention, reducing morbidity and mortality. Genetic counselling and regular follow-up are essential components of patient care in hereditary endocrine neoplasia.

Keywords: Multiple endocrine neoplasia type 2A (MEN2A), Medullary thyroid carcinoma (MTC), Pheochromocytoma, Primary hyperparathyroidism.

Received: 01-04-2025; **Accepted:** 27-05-2025; **Available Online**: 19-06-2025

1. Introduction

Multiple endocrine neoplasia type 2 (MEN2) is a rare genetic syndrome with endocrine tumours, including MTC, pheochromocytomas, and hyperparathyroidism caused by parathyroid adenoma or hyperplasia.[1,2] MEN2, caused by RET mutations, is inherited in autosomal dominant pattern with near 100% penetrance for Medullary Thyroid Carcinoma (MTC). It has three subtypes. The most common subtype, MEN2A, features MTC, bilateral pheochromocytomas, and hyperparathyroidism, with MTC often appearing first.[3] MEN2-related pheochromocytomas are bilateral, adrenal-specific tumours causing catecholamine excess, leading to hypertension, palpitations, and headaches.[4] Studies, including Niranjan et al.'s, highlight the unique features of bilateral adrenal lesions and stress timely adrenalectomy to prevent hypertensive crises.[5]

MTC is the first and most common manifestation of MEN2A, requiring early thyroidectomy, especially for high-risk RET mutations. Yasir et al. highlight genetic testing to confirm diagnosis, assess risk, and guide treatment.[3]

Parathyroid adenomas or hyperplasia can lead to hypercalcemia and associated complications.[6] The coexistence of MTC, pheochromocytomas, and hyperparathyroidism poses diagnostic and management challenges, particularly in resource-limited settings.[7] Niranjan et al. highlight the need for a multidisciplinary

*Corresponding author: Jyoti Verma
Email: dr.jyotiv1@gmail.com

https://doi.org/10.18231/j.ijpo.2025.043

approach in MEN2A, focusing on early diagnosis, imaging, and timely surgery for better outcomes.[5]

Genetic screening is key to diagnosing MEN2A, confirming RET mutations and enabling early detection in at-risk family members.[8]

2. Case Description

A 42-year-old male businessman from Lucknow presented with episodic burning abdominal pain lasting 4–5 years, occurring every 2–3 months. The episodes were accompanied by paroxysmal palpitations occurring 1–2 times every 10–12 days, severe hypertension with a peak recording of 210/100 mmHg, and a recent episode of chest pain with a sense of impending doom. The patient did not report fever, nausea, vomiting, tremors, exertional dyspnoea, syncope, hypokalaemia, or any signs of hypercortisolism.

On clinical examination, the patient was alert, cooperative, and well-oriented, with a BMI of 21.7 kg/m². Blood pressure was measured at 130/78 mmHg, and the pulse rate was recorded as 89 beats per minute. A firm, well-defined thyroid nodule measuring 2×1 cm was palpable in the left lobe of the thyroid. Abdominal and systemic examinations were unremarkable, with no palpable masses or tenderness noted.

Biochemical testing revealed elevated plasma catecholamine levels, consistent with pheochromocytoma. Thyroid and parathyroid function tests showed abnormalities suggestive of medullary thyroid carcinoma and primary hyperparathyroidism.

Targeted ultrasound of the thyroid demonstrated multiple hypo- to isoechoic lesions, with the largest lesion in the left lobe measuring 18×17 mm, categorized as TIRADS 4. A hypoechoic lesion measuring 6×4 mm was identified below the right thyroid lobe, suggestive of a parathyroid adenoma. Imaging studies, including Contrast enhanced computed tomography scan (CECT) images, demonstrated bilateral adrenals enlargement with left adrenal measuring 11×10×9 cm and right measuring 7.5×6.5×4 cm. (**Figure 1**) Ga-68 DOTANOC Positron emission tomography scan (PET-CT) demonstrating avid uptake in the bilateral thyroid nodule inferior to the left lobe of the thyroid on a technetium-99 Sestamibi scan and increased uptake in the bilateral adrenal lesions, consistent with catecholamine-secreting tumours.(**Figure 1**)

On FNAC (Fine needle aspiration cytology) smears show sheets as well as clusters of rounds to oval atypical follicular epithelial cells with coarsely clumped chromatin and amphophilic granular cytoplasm. Fair number of plasmacytoid cells are also seen. (**Figure 1**) The bilateral thyroid nodules were reported as suspicious of malignancy (Bethesda Category V) and possibility of for medullary thyroid carcinoma was considered.(**Figure 1**)

The patient underwent open transperitoneal bilateral adrenalectomy, total thyroidectomy, cervical lymph node dissection, and right inferior parathyroidectomy. During the adrenalectomy, the left adrenal gland, measured 11×10×9 cm and weighed 518 grams, displayed lobulated tan-coloured areas with regions of haemorrhage and necrosis. The right adrenal gland, measuring 7.5×6.5×4 cm and weighing 54 g, exhibited similar gross findings. (**Figure 2**) Histopathological examination of the bilateral adrenals confirmed the diagnosis of bilateral pheochromocytoma. The tumour cells exhibited mild pleomorphism and mitotic activity, yielding Pheochromocytoma diagnosis of the Adrenal Gland Scaled Score (PASS) of 1. (**Figure 2**) FNAC findings and was reported as Genetic testing confirmed the presence of a RET C634R mutation, diagnostic for MEN2A.

Subsequent surgery included total thyroidectomy with central and selective lateral neck dissections. Histopathology revealed medullary thyroid carcinoma with C-cell hyperplasia, metastatic medullary thyroid carcinoma in multiple lymph nodes, and parathyroid adenoma in the right inferior parathyroid gland. The total thyroidectomy revealed medullary thyroid carcinoma with C-cell hyperplasia, consistent with MEN2A. Cervical lymph node analysis identified metastatic medullary thyroid carcinoma in 10 of 11 central nodes, 5 of 8 left selective nodes, and 2 of 8 right selective nodes.**(Figure 2)** The right inferior parathyroidectomy confirmed the presence of a parathyroid adenoma measuring 0.7×0.5 cm on histopathological examination. (**Figure 2**)

Post-operative recovery was uneventful. The patient demonstrated stable vital signs and was monitored for adrenal insufficiency and hypocalcemia, which were managed appropriately with hormone replacement therapy. Follow-up biochemical markers showed normalization of plasma catecholamine level and serum calcitonin levels, indicating effective tumour removal. The patient was discharged in stable condition with endocrinology follow-up scheduled for ongoing surveillance. Regular monitoring was advised for serum calcium, parathyroid hormone, calcitonin and carcinoembryonic antigen (CEA) levels. The patient was also counselled regarding the hereditary nature of MEN2A, and genetic screening of first degree relatives was initiated.

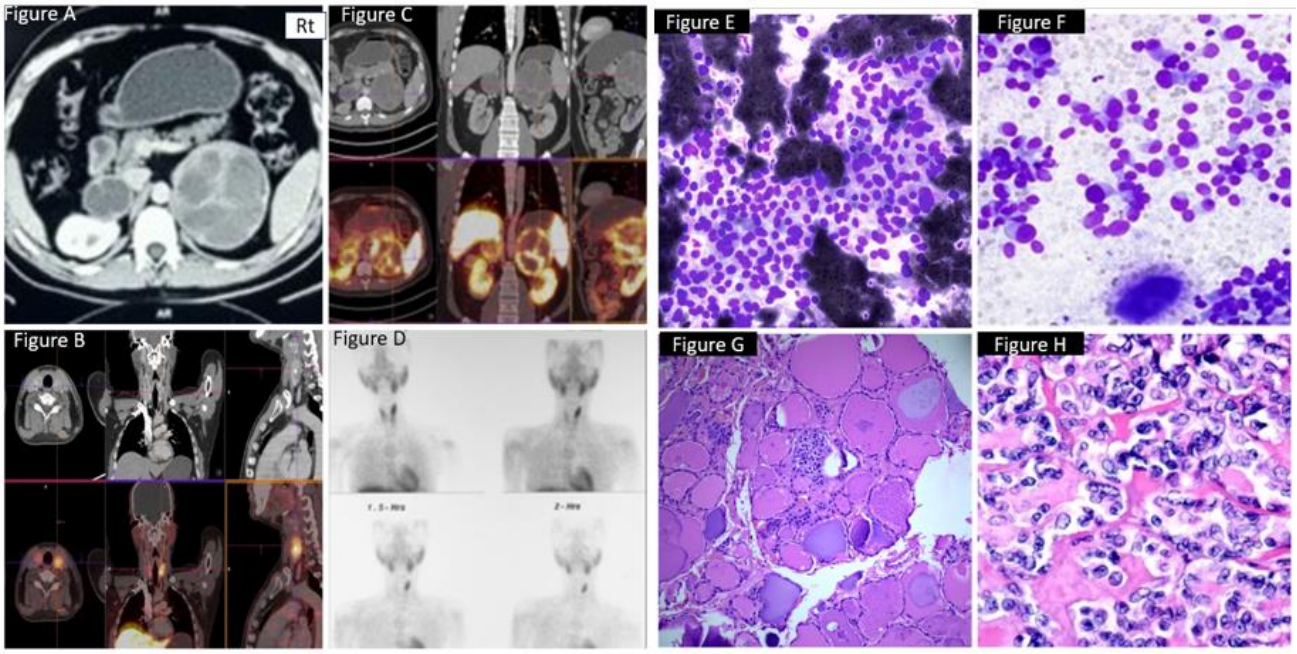

Figure 1: **A)**: Contrast-enhanced CT (CECT) of the abdomen revealed bilateral adrenal masses with soft tissue attenuation and smooth margins. The right adrenal gland measured 5.4×5.3 cm, while the left adrenal gland was larger at 10.5×8.2 cm. **B):** PET-CT scan of the neck showing uptake in thyroid nodules and metastatic cervical lymph nodes. **C):** Ga-68 DOTANOC PET-CT showing avid uptake in bilateral adrenal masses (SUV Max 18.5, left > right); **D):** Sequential scintigraphic imaging in MEN2A syndrome: Images obtained at 10 minutes, 45 minutes, 1.5 hours, and 2 hours post-injection demonstrate progressive radiotracer uptake in the affected regions, consistent with functional adrenal or thyroid pathology. **E):** Cytology smear showing sheets of round to oval tumour cells with coarsely clumped chromatin and amphophilic granular cytoplasm (MGG,x200). **F):** Smear showing tumour cells arranged in small clusters as well as scattered singly lying cells which are round to plasmacytoid (MGG, x400). **G):** Thyroid gland with C-cell hyperplasia (H&E, x400). **H):** Thyroid gland showing medullary thyroid carcinoma (H&E, oil immersion)

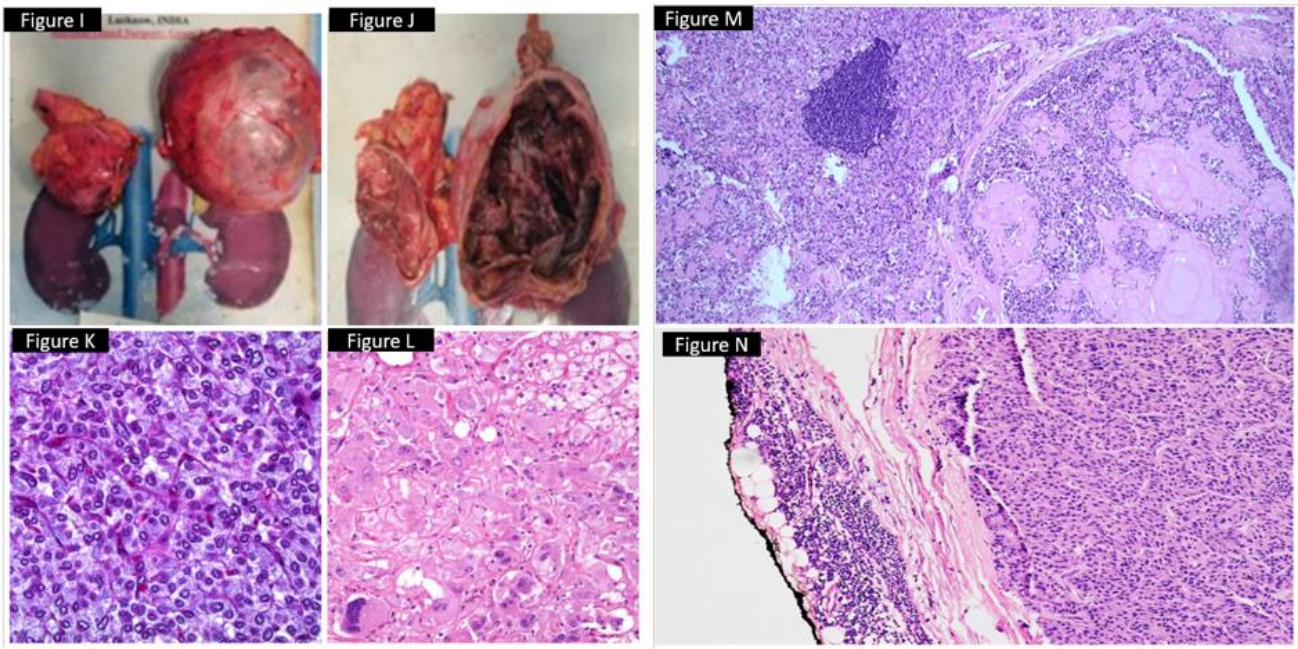

Figure 2: **I):** Gross specimen of adrenal glands showing a significantly larger left adrenal gland compared to the right; **J):** Cross-section of adrenal glands showing hemorrhagic and necrotic areas in the left adrenal pheochromocytoma. **K)**: Right adrenal gland-High-power view showing large polygonal cells with zellballen pattern (H&E, x200). **L):** Left adrenal gland-High-power view highlighting nuclear pleomorphism and mitotic activity (H&E, x400). **M)**: Cervical lymph node showing metastatic medullary thyroid carcinoma. (H&E, x100). **N):** Right inferior parathyroid gland showing parathyroid adenoma, composed of chief cells having round nucleus with granular cytoplasm: (H& E, x100)

3. Discussion

MEN2A is a hereditary syndrome caused by germline mutations in the RET proto-oncogene, which leads to the development of medullary thyroid carcinoma (MTC), pheochromocytomas, and primary hyperparathyroidism. This case highlights the challenges and complexities of managing MEN2A in a 42-year-old male with bilateral adrenal pheochromocytomas, metastatic medullary thyroid carcinoma, and a parathyroid adenoma. The findings underscore the importance of integrating clinical, genetic, imaging, and histopathological data for optimal diagnosis and management.

MEN2A is characterized by a nearly 100% lifetime risk of developing MTC, with pheochromocytomas occurring in 50% of cases and primary hyperparathyroidism in 20–30% of cases.[9] The RET C634R mutation identified in this case is one of the most common mutations associated with MEN2A, conferring a high risk for aggressive MTC and bilateral pheochromocytomas.[10] Genetic testing is pivotal for confirming MEN2A, as it enables early diagnosis, risk stratification, and familial screening.[11]

Preoperative evaluation revealed elevated catecholamines confirming pheochromocytoma, and increased calcitonin levels suggesting a medullary thyroid carcinoma. Parathyroid hormone and calcium levels were also raised, indicating hyperparathyroidism. These findings guided alpha-blockade initiation reducing perioperative risks and ensuring effective treatment of all MEN2A components.

Bilateral pheochromocytomas, as seen in this case, are a hallmark of MEN2A and are distinguished from sporadic or von Hippel-Lindau (VHL)-associated pheochromocytomas by their higher likelihood of being bilateral and confined to the adrenal glands.[12] Imaging studies, including Ga-68 DOTANOC PET-CT in this case, demonstrated avid uptake in the bilateral adrenal lesions, consistent with catecholamine-secreting tumours.

Histopathological analysis of MEN2A-related pheochromocytomas reveals distinct features such as large, polygonal tumour cells with eosinophilic granular cytoplasm and hyaline globules, observed in nearly all cases.[13] In contrast, sporadic pheochromocytomas often lack these defining features. The findings of nuclear gigantism and minimal stromal involvement further corroborate the diagnosis. These pathological characteristics are critical for distinguishing MEN2A from other syndromic and sporadic causes of adrenal tumours.[14]

MTC, the earliest manifestation of MEN2A, arises from parafollicular C-cells of the thyroid and has a high propensity for early metastasis to cervical lymph nodes, as evidenced in this case. The histological findings of C-cell hyperplasia and amyloid deposits are hallmark features of MEN2-associated MTC. Studies emphasize the aggressive nature of MTC in RET mutation carriers, necessitating early thyroidectomy to prevent metastatic progression.[15]

Surgical intervention is the cornerstone of MEN2A treatment. In this case, bilateral adrenalectomy was performed to address the pheochromocytomas, while total thyroidectomy and cervical lymph node dissection were carried out for metastatic MTC. Preoperative alpha-adrenergic blockade was critical for stabilizing blood pressure and preventing intraoperative hypertensive crises, as recommended in MEN2 management guidelines.[16] The importance of lymph node dissection in cases of metastatic MTC, as seen in this patient, cannot be overstated. Studies have shown that comprehensive lymphadenectomy improves local disease control and reduces the risk of recurrence.[17]

Parathyroidectomy was performed to manage primary hyperparathyroidism caused by a parathyroid adenoma. Although less common in MEN2A, hyperparathyroidism adds complexity to the surgical approach. Intraoperative parathyroid hormone monitoring, as employed here, helps minimize the risk of postoperative complications like hypocalcemia.[18]

This case aligns with findings from Indian tertiary care centres reported by Niranjan et al., which highlight the unique clinical and pathological features of MEN2A-related adrenal lesions.[5] Bilateral involvement, histological features such as hyaline globules, and the necessity of adrenalectomy are consistent findings. Furthermore, studies emphasize the critical role of early genetic testing and timely surgical intervention in improving outcomes in MEN2A patients.[19]

MEN2A requires lifelong surveillance to monitor for recurrence or new tumour development. Post-surgical follow-up includes regular measurement of serum calcitonin and carcinoembryonic antigen (CEA) for MTC, plasma metanephrines for pheochromocytomas, and serum calcium for parathyroid function. As emphasized in studies a tailored follow-up strategy based on mutation type, disease burden, and surgical outcomes is essential to improve prognosis.[20]

Thorough evaluation is essential in endocrine tumours like MEN2A to ensure accurate diagnosis, prevent life-threatening complications, and guide surgical management. Comprehensive assessment-including clinical, biochemical, imaging and genetic testing- detects associated tumours such as medullary thyroid carcinoma, pheochromocytomas and hyperparathyroidism.

Genetic testing is vital in MEN2A management for earIy diagnosis, risk stratification and personalized treatment. Identifying RET mutations confirms the condition, enables early intervention and family screening. It also informs surgical planning and the need for preoperative measures. Establishing a diagnostic baseline allows for lifelong surveillance using markers like calcitonin, CEA, and calcium levels. Overall, a multidisciplinary approach improves

patient outcomes, reduces morbidity, and supports preventive care for at-risk relatives.

4. Strengths

The strength of this case lies in its comprehensive and multidisciplinary approach to the diagnosis and management of MEN2A, integrating genetic, biochemical, radiological, and histopathological data. This approach allowed for timely and effective treatment, improving patient outcomes and facilitating familial screening.

5. Limitations

While the case underscores the importance of genetic testing and multidisciplinary management, the absence of a family history or related history in this patient might indeed limit the broader generalizability of findings in the study. This could also make familial screening recommendations less relevant for such patients. Also, as a single report, the findings may not be generalizable to all MEN2A presentations. Long term follow-up data is also limited at this stage, and broader studies are necessary to validate the management strategies described here.

6. Conclusion

This case highlights the complexity and multidisciplinary nature of diagnosing and managing MEN2A, a rare hereditary syndrome characterized by medullary thyroid carcinoma, bilateral pheochromocytomas, and primary hyperparathyroidism. The integration of genetic testing, advanced imaging modalities, and histopathological evaluation was pivotal in confirming the diagnosis and guiding effective surgical interventions, including bilateral adrenalectomy, total thyroidectomy, and parathyroidectomy. Early recognition of MEN2A through RET mutation testing not only allows timely treatment but also facilitates familial screening, enabling preventive strategies for at-risk individuals. This case underscores the critical importance of a comprehensive and proactive approach to MEN2A, emphasizing lifelong surveillance to monitor for recurrence or new tumour development, ultimately improving patient outcomes and quality of life.

7. Abbreviations

MEN2A: Multiple Endocrine Neoplasia Type 2A; MTC: Medullary Thyroid Carcinoma; CT: Computed Tomography; FNAC: Fine Needle Aspiration Cytology; PASS: Pheochromocytoma of the Adrenal Gland Scaled Score; VHL: Von Hippel-Lindau; CEA: Carcinoembryonic Antigen.

8. Clinical Significance

This case underscores the importance of timely diagnosis and management of MEN2A, emphasizing the role of RET mutation testing in confirming the diagnosis and facilitating familial screening. The integration of advanced imaging, histopathological evaluation, and surgical interventions, including adrenalectomy and thyroidectomy, underscores the importance of a multidisciplinary approach in preventing life-threatening complications. Proactive management and lifelong surveillance are essential to improving outcomes and reducing the burden of MEN2A in affected families.

9. Source of Funding

None.

10. Conflicts of Interest

Authors declared that there is no conflict of interest.

References

1. Kamilaris CDC, Stratakis CA. Multiple Endocrine Neoplasia Type 1 (MEN1): An Update and the Significance of Early Genetic and Clinical Diagnosis. *Front Endocrinol (Lausanne)*. 2019;10:339.
2. Marini F, Falchetti A, Del Monte F, Carbonell Sala S, Gozzini A, Luzi E, et al. Multiple endocrine neoplasia type 1. *Orphanet J Rare Dis*. 2006;2;1:38.
3. Yasir M, Mulji NJ, Kasi A. Multiple Endocrine Neoplasias Type 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jan 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK519054/
4. Gupta PK, Marwaha B. Pheochromocytoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jan 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK589700/
5. Niranjan G, Prasad P, Gupta N, Agrawal V, Mishra A, Jain N, et al. Characteristics of Bilateral Adrenal Lesions: Experience from an Indian Tertiary Care Centre. *Indian J Endocrinol Metab*. 2024;28(3):273–8.
6. Ungureanu S, Şipitco N, Alexa Z, Gonța V, Bujac M, Parnov M, et al. MEN 2A syndrome – Multiple endocrine neoplasia with autosomal dominant transmission. *Int J Surg Case Rep*. 2020;73:141–5.
7. Alevizaki M. Management of hyperparathyroidism (PHP) in MEN2 syndromes in Europe. *Thyroid Res*. 2013;6 Suppl 1(Suppl 1):S10.
8. Paun D, Tilici D, Paun S, Mirica A. Prospective Genetic Screening in Multiple Endocrine Neoplasia Syndromes. *Children (Basel)*. 2024;11(8):1012.
9. Miyashita H, Yuen T. Parathyroid Gland Diseases. In: Zaidi M, editor. *Encyclopedia of Bone Biology* [Internet]. Oxford: Academic Press; 2020 [cited 2025 Jan 21]. p. 65–74.
10. Walczyk A, Zgubieński K, Chmielewski G, Hińcza-Nowak K, Kowalik A, Jaskulski J, et al. Late-Onset Medullary Thyroid Cancer in a Patient with a Germline *RET* Codon C634R Mutation. *Diagnostics (Basel)*. 2021;11(8):1448.
11. Eng C, Plitt G. Multiple Endocrine Neoplasia Type 2. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2025 Jan 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1257/
12. Schreinemakers JMJ, Zonnenberg BA, Höppener JWM, Hes FJ, Borel Rinkes IHM, Lips CJM. A patient with bilateral pheochromocytoma as part of a Von Hippel-Lindau (VHL) syndrome type 2C. *World J Surg Oncol*. 2007 Oct 8;5:112.
13. Efared B, Atsame-Ebang G, Tahirou S, Mazaz K, Hammas N, El Fatemi H, Chbani L. Bilateral pheochromocytoma with ganglioneuroma component associated with multiple neuroendocrine neoplasia type 2A: a case report. *J Med Case Rep*. 2017;11(1):208.
14. Cerny JC, Jackson CE, Talpos GB, Yott JB, Lee MW. Pheochromocytoma in multiple endocrine neoplasia type II: an

example of the two-hit theory of neoplasia. *Surgery.* 1982;92(5):849–52.
15. de Groot JW, Links TP, Hofstra RMW, Plukker JTM. An Introduction to Managing Medullary Thyroid Cancer. *Hered Cancer Clin Pract*. 2006;4(3):115–25.
16. Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B. Incidentally discovered adrenal masses. *Endocr Rev*. 1995;16(4):460–84.
17. Giusti F, Marini F, Brandi ML. Multiple Endocrine Neoplasia Type 1. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2025 Jan 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1538/
18. O'Riordain DS, O'Brien T, Grant CS, Weaver A, Gharib H, van Heerden JA. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. *Surgery.* 1993;114(6):1031–7.
19. Lairmore TC, Piersall LD, DeBenedetti MK, Dilley WG, Mutch MG, Whelan AJ, et al. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). *Ann Surg.* 2004;239(5):637–45.
20. Boukhannous I, Chennoufi M, Mokhtari M, El Moudane A, Barki A. Management of bilateral adrenal myelolipoma without endocrine disorder: About a rare case report. *Urol Case Rep*. 2021;39:101755.

Cite this article: Gupta N, Srivastava N, Verma J, Srivastava P. Comprehensive management of multiple endocrine neoplasia Type 2A (MEN2A): A multidisciplinary approach. *Indian J Pathol Oncol*. 2025;12(2):212–217.