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BRIEF REPORT

Expanding the phenotype of multiple endocrine neoplasia type 5 (MEN5): Pituitary gigantism, myelolipoma and familial pheochromocytoma due to a germline pathogenic *MAX* variant

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Abstract

Purpose Multiple endocrine neoplasia type 5 (MEN5) is an emerging syndrome of endocrine and non-endocrine tumors caused by germline pathogenic variants or genomic rearrangements of the *MAX* gene. Although *MAX* variants are predominantly associated with pheochromocytoma-paraganglioma (PPGL) risk, there are a growing number of associated tumors in other organs, including pituitary adenomas. We characterized the clinical presentation of various tumors in an extensive new kindred with a novel germline pathogenic variant of *MAX*.

Methods Clinical, genetic, pathological, radiological and hormonal investigations to identify and characterize disease status related to germline *MAX* gene sequence status.

Results We identified a novel germline pathological variant in exon 4 of the *MAX* gene, c.228delG, which was predicted to lead to a truncated protein (p.Asn78Thrfs*92). The propositus had developed pituitary gigantism due to a mixed growth hormone-prolactin secreting pituitary macroadenoma, which was controlled after two surgeries, medical therapy and radiotherapy. He subsequently developed bilateral and recurrent pheochromocytomas and following his death, an extra-adrenal myelolipoma was identified that was negative on MAX immunohistochemistry. An extensive history of pheochromocytomas or uncontrolled hypertension was present in the kindred and multiple affected and unaffected carriers of the c.228delG *MAX* pathogenic variant were characterized.

Conclusion We report the first case of pituitary gigantism in association with a pathogenic variant in the *MAX* gene, and characterize myeloplipoma as a new disease-association in MEN5. Increased awareness of MEN5 as a clinical entity and comprehensive screening of *MAX* pathogenic variant carriers can help to identify rare disease associations beyond PPGL.

Keywords MAX · Pituitary gigantism · Myelolipoma · Pheochromocytoma · Multiple endocrine neoplasia

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Introduction

Pituitary adenomas produce a variety of classical endocrine conditions depending on their cell of origin and growth characteristics [1]. Clinically-relevant pituitary adenomas occur with a prevalence of approximately 1 per 1000 of the general population, while the specific manifestations, such as acromegaly, Cushing's disease are individually rare [2]. Pituitary adenomas usually present as sporadic, isolated tumors in individuals without a personal or family history of endocrine neoplasia. They can also present in familial or hereditary settings like familial isolated pituitary adenomas, multiple endocrine neoplasia (MEN)-1, MEN4, Carney Complex and others [3]. Novel causes of sporadic and inherited isolated pituitary adenomas have recently emerged [4].

Pathogenic variants in genes associated with pheochromocytomas-paragangliomas (PPGL) may also cause pituitary adenomas [5, 6]. Among these is *MAX*, which is the partner of the transcription factor c-Myc, one of the most commonly dysregulated genes in cancer [7, 8]. Abnormalities affecting *MAX* are implicated in a wide range of cancers, like small cell lung cancer, gastrointestinal stromal tumors, and renal tumors [9–11]. Among *MAX*-related PPGL kindreds, pituitary adenomas also occur rarely [12–14]. Based on these findings, we and others have suggested that pathogenic *MAX* variants might represent a new neoplasia risk syndrome [13, 15], Termed "MEN5" by Seabrook et al, pathologists recently adopted this moniker in the draft World Health Organization 5th Edition of the Classification of Genetic Tumor Syndromes [13, 16]. Expanding the emerging phenotype further, we present a new MEN5 kindred with a germline pathogenic variant in *MAX* and familial pheochromocytoma and the first reported instances of pituitary gigantism and extra-adrenal myelolipoma.

Family details

The kindred is shown in Fig. 1. The propositus (III-9) had a medically unremarkable early childhood. During late childhood he experienced overgrowth, headaches, visual disturbance and sinusitis-like pain. Aged 11 he presented to another institution with gigantism, measuring 198 cm (>99% for height). He had elevated growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels and on magnetic resonance imaging (MRI) a pituitary macro-adenoma was reported. He underwent a transsphenoidal resection of the pituitary tumor which was confirmed as a mixed GH- and prolactin-positive adenoma. IGF-1 was controlled post-operatively, but at the age of 15 he presented again with acral enlargement and hyperhidrosis, accompanied by tumor regrowth and cavernous sinus invasion. GH, IGF-1 and prolactin were elevated. Medical therapy with intermittent subcutaneous octreotide injections and bromocriptine was started but hormonal control was not achieved. He underwent a second transsphenoidal surgery and gamma-knife radiotherapy. Biochemical remission was achieved and IGF-1 remained controlled thereafter.

At the age of 16 he complained of episodes of palpitations, sweating, and headaches with intermittent hypertension. Plasma normetanephrines were elevated >5-fold over normal. Abdominal imaging revealed a 1.9 cm left adrenal mass which had 50 Hounsfield units on computed tomography (CT). He underwent a resection of this mass, which was confirmed as a pheochromocytoma on pathology. Surgical resection led to symptomatic and biochemical normalization for five years, at which time palpitations, headache and sweating returned and plasma normetanephrines were again elevated (>4-fold over normal). An MIBG scan showed uptake in the right adrenal gland and he underwent an adrenalectomy which confirmed a right sided pheochromocytoma. He was supplemented with hydrocortisone and fludrocortisone and was again asymptomatic for five years. At that time his follow-up plasma normetanephrine was noted to be elevated. He had undergone an abdominal CT due to trauma and this revealed suspicious nodules in the left adrenal bed, but these were not visualized on MIBG scan. Surgical resection of the left adrenal bed lesions confirmed a recurrence of his pheochromocytoma. Post-operatively his plasma normetanephrine levels remained elevated at 1.4 ng/mL (upper limit of normal: <0.9 ng/mL), during sertraline treatment for anxiety, but he was otherwise asymptomatic. A 0.3 mg clonidine suppression test showed 42% suppression of plasma normetanephrine from baseline. A gallium DOTATATE scan showed a 1.4 cm lesion in the retroperitoneum medial to the left kidney and abutting the left postero-medial diaphragm. During follow-up the lesion remained stable, and owing to the patient's lack of symptoms and only mildly abnormal plasma metanephrines, he was followed by comprehensive imaging and biochemical surveillance every 6–12 months. At the age of 42, the patient died suddenly during recovery from routine orthopedic surgery. An autopsy found a 3 cm diameter tumor at the level of the pylorus of the stomach, corresponding to the lesion seen on imaging. There was no abnormal tissue in the adrenal beds and the pituitary fossa was empty.

Clinical data were collected from the kindred and genetic studies were offered following counselling and the provision of informed consent. The study was performed under the approval of the Ethics Committee of the University of Liège.

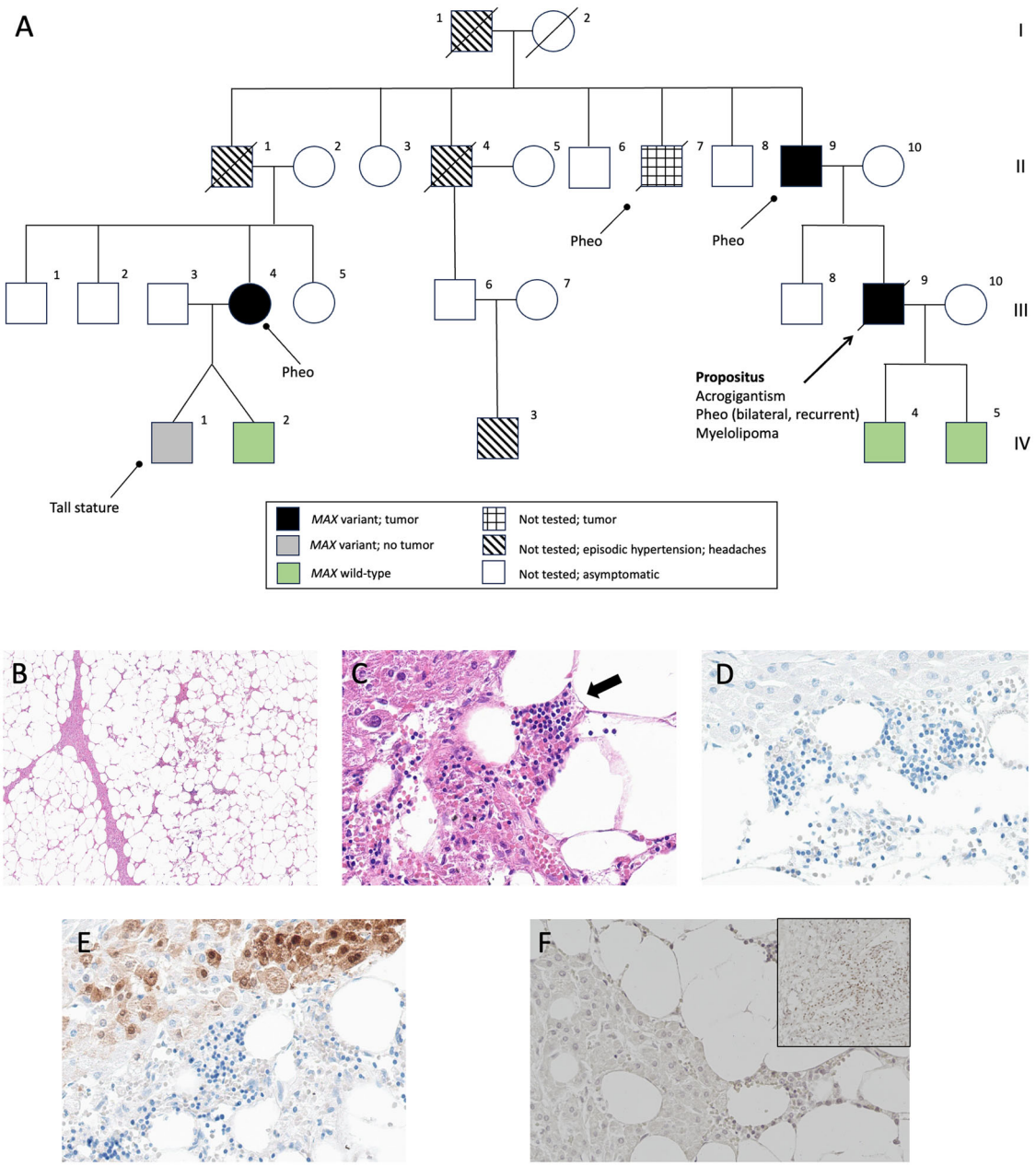

Fig. 1 **A** Family tree illustrating four generations of a kindred with a novel pathogenic germline *MAX* variant. The propositus is subject III-9. **B–F** Histological images from specimens of myelolipoma (Hematoxylin and Eosin-staining). (**B**) Low magnification showing mature fatty cells; (**C**) Hematopoietic cells (arrow) including myeloid and erythroid cells. In the left upper corner adrenocortical cells are apparent. (**D**) Negative staining for chromogranin A. (**E**) Positive immunohistochemical staining for CK18 reveals adrenocortical cells. (**F**) Immuno-histochemistry for MAX shows negative staining in the nuclei of erythroid, adipose and adrenal cortical cells; normal nuclear staining (brown) is seen in an adrenal sample from a patient with normal *MAX* sequence (inset)

Results

Genetic and clinical screening

Genetic testing was performed on the propositus using a 14-gene PPGL panel and this revealed a heterogeneous c.228delG variant affecting exon 4 of the *MAX* gene, which was predicted to lead to a p.Asn78Thrfs*92 protein truncation and loss of the C-terminal that is essential for MAX protein function. This variant (rs1555340550) did not appear in GnomAD; it was classified as pathogenic in ClinVar, on American College of Medical Genetics criteria (PVS1, PM2, PM6) and supported by other aggregated in silico evidence (AION platform, Nostos Genomics, Berlin Germany). His children were negative for the variant.

Clinical details showed that the father of the propositus (Fig. 1; II-9) had been diagnosed with a unilateral pheochromocytoma at the age of 45, that was surgically resected. Decades later he remains asymptomatic and had normal plasma metanephrines during follow-up. Genetic testing confirmed the c.228delG *MAX* variant. Three of the father's brothers were deceased and had a history of either pheochromocytoma (II-7), or episodic hypertension and headaches; (II-1; II-4). While all three had died before genetic testing could be performed, individual II-1 is an obligate carrier as his daughter (III-4) carries the familial c.228delG *MAX* variant and was affected by a unilateral (right-sided) pheochromocytoma aged 35. Recent imaging with ^{68}Ga-DOTATATE PET-CT, abdominal and pituitary MRI and subsequent hormonal profiles showed only mild non-enhancing nodularity in left adrenal and non-specific hepatic calcifications. Her offspring are fraternal twin males, one of whom (IV-1) is a carrier of the familial *MAX* variant and is tall (200 cm). His pituitary MRI, thoraco-abdomino-pelvic CT and hormonal testing were completely normal. Subject IV-3 has a history of episodic hypertension and headache but has not undergone genetic testing; as noted above his deceased grandfather (II, 4) also had a similar history.

Pathology

Study of the abdominal tumor identified at post-mortem showed no evidence of pheochromocytoma/paraganglioma. On histology, there was a mixture of nodular, highly differentiated univacuolar adipose tissue, with clusters of erythrocytes mixed with nucleated erythrocytes seen between the adipocytes (Fig. 1B). Interspersed with the tissue were multifocal band-like epithelial cell clusters. These were consistent with adrenocortical cells with heterogeneous CK18 and low melanin A and inhibin positivity. The cytoplasm was mainly granular-eosinophilic with focally bright areas. The epithelioid cell clusters were negative for synaptophysin and chromogranin A. Immunohistochemical staining for MAX was negative in the tumoral tissue. The diagnosis was consistent with an myelolipoma occurring in an ectopic adrenal rest.

Discussion

Since its identification as a risk gene for PPGL in 2014, results point to a broader tumor risk pattern associated with pathogenic *MAX* variants. Among the associated tumors reported are pituitary adenomas, primarily somatotropinomas and prolactinomas. In the current study we report the first case of pituitary gigantism to occur in the setting of a germline pathogenic *MAX* variant, thereby adding a new germline genetic cause for pituitary gigantism. Including the current case, 13 MAX-associated pituitary adenomas have been reported [12, 13]; see [14] for review. They are equally divided by sex and as familial/sporadic presentation. Patients most frequently had either GH/IGF-1 excess (39%) or prolactinomas (31%); 46% were macroadenomas at diagnosis. Patients were diagnosed in their early to mid 20's. Pituitary adenomas were diagnosed before or simultaneously with a pheochromocytoma in half of cases. In the current case the initial pathology showed a mixed GH/ prolactin positive pituitary adenoma, which occur in other genetic forms of gigantism [17]. Due to their rarity, the status of MAX immunohistochemical staining in pituitary tissue remains to be characterized.

Myelolipomas are benign tumors consisting of mature adipose tissue and hematopoietic (myeloid) cells. They usually occur in the adrenal cortex but rarely extra-adrenal myelolipomas have been described throughout the abdominal cavity and elsewhere [18]. Myelolipomas are of unknown etiology, although the range of potential causes is wide. About 10% of myelolipoma patients also have congenital adrenal hyperplasia [18]. The myelolipoma arose in an ectopic adrenal rest, which is an unusual presentation. Ectopic adrenal tissue, classically testicular, can itself be associated with CAH, particularly in poorly-controlled cases [19]. In the current case, the patient did not have evidence of CAH or adrenocortical disease. Staining for MAX in the myelolipoma was absent (in all tissue subtypes), which supports an etiological role and adds myelolipoma as a novel *MAX*-associated finding.

Since its original discovery *MAX* has evolved from a purely PPGL risk gene into a more complex syndrome [7, 12, 13]. The 2022 WHO Classification of Familial Endocrine Tumor Syndromes included "MEN5" due to germline variants in the *MAX* gene [16]. In the absence of systematic studies in larger PPGL and other case collections, much of the information on MEN5 comes from individual case reports, like the current one. Recent data from a large study in Marseilles has shown, for instance, that *MAX* variants are not found in sporadic isolated pituitary adenomas [20]. The full profile of tumoral and non-tumoral risks in MEN5 is unclear, as is the lifetime penetrance and the order of appearance of different linked tumors. For instance, pituitary lesions can predate, occur simultaneously or follow the diagnosis of pheochromocytomas [16]. It is likely that greater clarity on disease associations and their varied presentations will come with more extensive clinical studies of *MAX*-affected kindreds.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions A.H. and J.S. collected clinical data; H.M., A.K. and N.S.P. performed pathology studies; A.H., J.S., A.B., P.P., and A.F.D. analysed results; A.F.D. and A.H. designed the study and wrote all versions of the manuscript and figures. All authors reviewed the manuscript.

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