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Pheochromocytomas: Are They Still the 10% Tumor?

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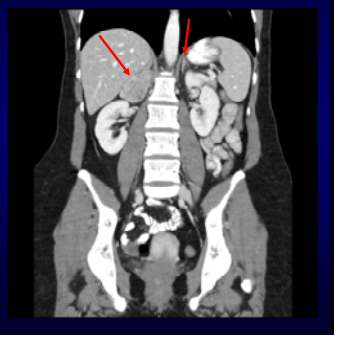
Case Presentation: 47 yo woman

- CC: Hematuria
- HPI: Nocturia and flank pain
- PMHx: Thyroid Nodule
- PSHx: Ovarian Cystectomy
- Meds: none
- FHx: M – breast ca, F – lung ca
- SHx: Married. Denies Tobacco/alcohol/Drugs
- ROS: palpitations, anxiety, headaches, depression, insomnia, and unusual vibratory sensation

Case Evaluation

1. Stress test
   - Negative
2. CT scan
   - Large right adrenal mass



Case: Pheo Work-up

1. Blood tests
   - ChromA 295 (<225)
2. 24 hour urine screening
   - Metanephrines 422 (30-180)
   - Normetanephrines 716 (119-451)
   - Dopamine >25,162 (52-480)
3. Presumed Diagnosis: Dopamine-secreting adrenal pheochromocytoma
4. Phenoxybenzamine started
5. Surgery → Laparoscopic Adrenalectomy

Case: Post-Op Evaluation

- Path: 8.5 cm pheochromocytoma
- Post-operative visit: Majority of preoperative symptoms resolved
- Genetic testing recommended

Case: Genetic Screening

- VHL mutation found
  - 241C>T
  - Pro81Ser
- VHL work-up
  - Ophthalmology exam – normal
  - Brain MRI – normal
  - Spine MRI – T7 hemangioblastoma
  - Children tested – negative
  - Siblings – notified

Study Hypothesis

- We hypothesized:
  - The historic "10% rule" for pheochromocytoma (Pheo) would not hold up based on recent literature
  - The rates of bilaterality, malignancy, and association with hereditary syndromes would be different
    - Improvements in medical imaging
    - Accessibility to gene testing

Study Aims

- To retrospectively evaluate a large, single institution cohort of patients who underwent adrenalectomy for Pheo
  - For patients treated in a newer vs. older decade, we calculate and compare rates of:
    - Bilaterality
    - Malignancy
    - Inherited Syndromes

Study Methods

- Identified all patients who received initial adrenalectomy for Pheo between 1/1/1990-12/31/2010
  - Excluded extra-adrenal Pheos
  - Excluded patients with known VHL, MEN2, NF1, SDHD and SDHB syndromes
- Classified 2 cohorts
  - Early: January 1, 1990 – December 31, 1999
  - Late: January 1, 2000 – December 31, 2010

Genotype–Phenotype Correlations of Pheochromocytoma in Two Large von Hippel–Lindau (VHL) Type 2A Kindreds With Different Missense Mutations

Sarah M. Nielsen,[1] Wendy S. Rubinstein,[2,3] Darcy L. Thull,[4] Michaele J. Armstrong,[5] Eleanor Feingold,[1] Michael T. Stang,[5] James R. Gnarra,[6] and Sally E. Carty[1]*

	Family 1	Family 2
Germany	East Central	Black Forest
Exon	1	1
VHL Mut.	Y112H	Y98H
Generations	7	6
Members	107	131
Pheos	65	65

	Family 1	Family 2
Patients	30	33
Mean Age	29	20
Multifocal	60%	40%
Malignant	20%	5%
Fatal	17%	0%
Extra-Adrenal	14%	28%

Comparison of 2 Large VHL Kindreds: Penetrance and Phenotype

	Members	VHL 2A	Clinically Affected	Obligate Carrier	Genetic Only
Family 1	107	46%	71%	12%	16%
Family 2	131	50%	72%	12%	15%

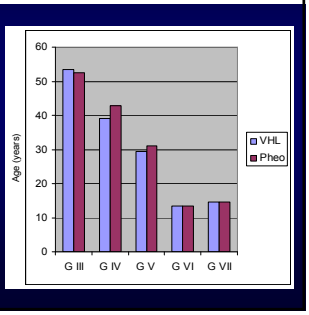
	Pheo	HB	RA	RCC	Panc Cyst
Family 1	70%	15%	33%	3%	3%
Family 2	66%	23%	17%	2%	0%

Nielsen SM, et al. AJMG, 2010.

Long-term outcomes, branch-specific expressivity, and disease-related mortality in von Hippel-Lindau type 2A

Sarah M. Nielsen · Wendy S. Rubinstein · Darcy L. Thull · Michaele J. Armstrong · Eleanor Feingold · Linwah Yip · Samuel A. Tisherman · Sally E. Carty

- Patriarch came from Saxony in 1670
- Total: 11 branches w. 644 kindred members
- VHL affected: 3 branches w. 107 at risk kindred members
- Disease-related mortality decreases with generations



Branch-specific Expressivity

	Branch II-2	Branch II-3	Branch II-4
VHL Diagnosis	32%	30%	63%
Clinically Affected	78%	78%	68%
Pheo	86%	43%	100%
Pheo Only	0%	29%	81%
Retinal Angioma	86%	83%	11%
RA Only	14%	67%	0%

Nielsen SM, et al. Fam Cancer, 2011.

Summary: Pheo Phenotype of 2 VHL kindreds

- Y112H:
  - Mean age at Pheo diagnosis is 29 years
  - Decreased mortality over time
  - Pheos are mutifocal, malignant, and mortal
- Y98H:
  - Mean age at Pheo diagnosis is 20 years
  - 80% Pheo penetrance by age 50
  - Young, unifocal, and extra-adrenal

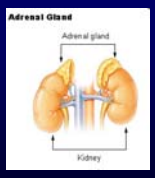
Nielsen SM, et al. AJMG, 2010.

Study Results: Demographics of Seemingly Sporadic Pheo Cohort

	Early	Late	*p*-value
Surgeons	1	7	--
Hospitals	1	4	--
Patients	11	62	--
Pheos	12	67	--
Male	45%	39%	0.67
Age (yrs)	44	48	0.42
Size (cms)	5.3	4.7	0.48

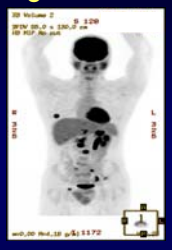
Results: Pheo Laterality

	Early	Late	p-value
Right	45%	48%	0.86
Bilateral	9%	8%	0.91



Results: Incidence of Malignant Pheo

- *Malignant* Pheo if lymph node or distant metastasis diagnosed histologically, or by abnormal MIBG uptake with elevated urine or plasma metanephrines at presentation or on postop follow-up



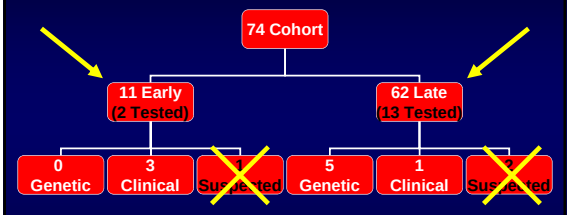
	Early	Late	Cohort	*p*-value
Malignant, # pts	2 (18%)	2 (3%)	4 (5%)	0.04
Mean follow-up (mos)	107	29	42	0.0001

Results: Time to Diagnosis of Malignancy

	Pt. (sex; age)	Pheo size (cm)	Location of Mets	Mos. to Recur
Early #1	F; 39	2.4	Intra-abd	83
Early #2	M; 40	16.5	Bone	140
Late #1	M; 48	9	Peri-aortic and MS LNs	8
Late #2	M; 19	NA	Bone, Liver, Lung, LNs	119

- Mean time to malignancy = 88 months
- Mean FU: early, 107 months and late, 29 months

Results: Evaluation for Genetic Syndromes



	Early	Late	Cohort	p-value
Genetic Testing	18%	21%	21%	0.83
Hereditary	27%	10%	12%	0.06

Results: Associated Syndromes in Early Cohort

Pt	Syndrome	How Dx?	GT Results	Additional Manifestations
1	MEN2	Clinically	RET neg	Parathyroid Hyperplasia
2	NF1	Clinically	NA	Neurofibromas
3	VHL	Clinically	NA	RCC
4	VHL	--	NA	FHx of RCC

Results: Late Cohort Syndromes

Pt	Syndrome	How Dx?	GT Results	Add. Manifestations
1	MEN2A	GT	Y791F	None
2	MEN2A	GT	C634R	MTC
3	MEN2B	Clinically	M918T	MTC, meningioma
4	SDHB	GT	Leu111SerfsX7	None
5	VHL	GT	Pro81Ser	Hemangioblastoma
6	MEN2A	Clinically	Partial RET -	MTC, HPTH
7	VHL	--	NA	New renal lesion
8	NF1	--	NA	FH of café au lait spots

Results: Genetic Syndromes

	Early	Late	Cohort
Positive	27%	10%	12%
MEN2A/2B	1	4	5
NF1	1	0	1
SDHB	0	1	1
VHL	1	1	2
Total	3	6	9

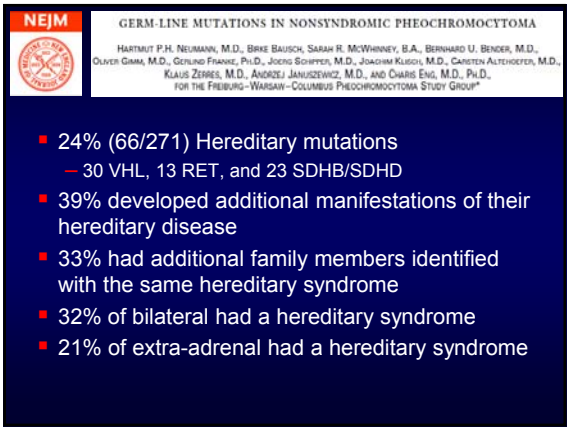
Results: Bilaterality and Malignancy are Associated with Hereditary Syndromes

- Bilateral
  - 50%
- Unilateral
  - 9%
- P=0.009

- Malignant
  - 50%
- Non-malignant
  - 12%
- P=0.02

Study Limitations

- ~20% (15/73) of patients were compliant with genetic testing
- But, when testing was performed, 33% (5/15) of patients had positive results
  - Selection bias
- Shorter follow-up in the late cohort



- 24% (66/271) Hereditary mutations
  - 30 VHL, 13 RET, and 23 SDHB/SDHD
- 39% developed additional manifestations of their hereditary disease
- 33% had additional family members identified with the same hereditary syndrome
- 32% of bilateral had a hereditary syndrome
- 21% of extra-adrenal had a hereditary syndrome

Study Conclusions

1. The rate of bilateral pheochromocytoma has remained at 10%, despite modern imaging techniques
2. With long-term follow-up, malignant Pheo is diagnosed in at least 18% of patients

Study Conclusions

3. Inherited syndromes were diagnosed in 12% of seemingly sporadic Pheo.
   Patient compliance with recommended genetic testing was low (20%) but when performed, 33% had positive results.
4. Inherited syndromes were more common in patients with bilateral tumors, but are also diagnosed in patients with unilateral Pheo.
5. Genetic testing should be considered for all Pheo patients.

Thank You

Questions?