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A case of multifocal, malignant paraganglioma of the head and neck

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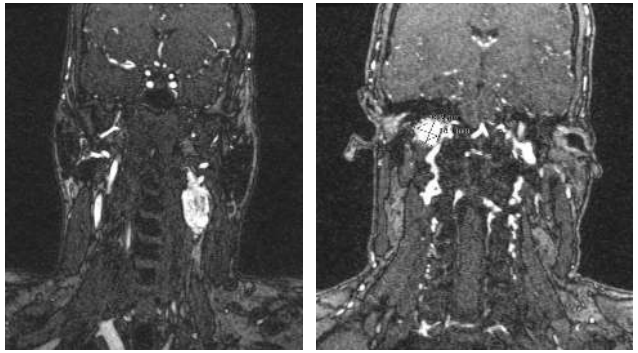
BACKGROUND

Most head and neck paragangliomas (PGL) are benign with malignancy being reported in less than 4% of the cases. Malignant PGL can be indolent or aggressive. The location of these tumors can make surgical resection difficult.

CASE PRESENTATION

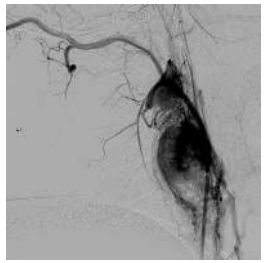
A 37 year old man underwent a CT scan of head and neck following a motor vehicle accident that showed a incidental finding of a 5.5 cm x 2.5 cm mass at the left carotid bifurcation causing effacement of the jugular vein.
No personal or family history of malignancy

MRI of neck showed multiple tumors
- Let carotid bulb (3.6 x 2.7 cm)
- Left glomus vagale (1.7 cm)
- Right glomus jugulare (1.6 cm)
- Right glomus vagale (5 mm)
- Right carotid bulb (1 cm)



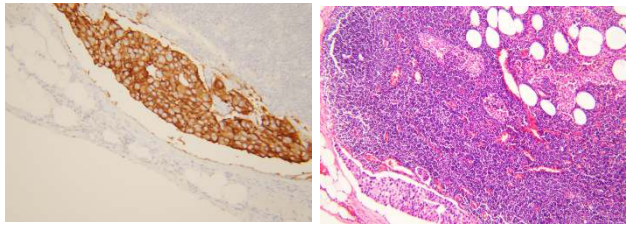
MRI of the neck showing multiple masses

- Pre-operative embolization of the left glomus jugulare tumor was performed with 80% reduction in the tumor burden

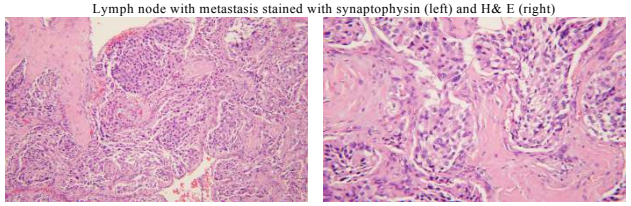


Embolization of the glomus jugulare tumor

- Resection of left carotid body tumor and level 2 and 3 lymph node dissection was done.
- Pathology revealed malignant paraganglioma metastatic to 1 lymph node. SDHB staining was absent suggestive of the presence of an SDHx mutation.
- Post-resection PET CT showed ill-defined activity along the surgical bed, increased activity seen in the right base of skull jugular bulb region and no evidence of metastatic disease.
- Genetic testing revealed SDHD mutation.
- Adjuvant radiation therapy to the left neck and primary radioablation of the right sided masses was recommended.



Lymph node with metastasis stained with synaptophysin (left) and H& E (right)



DISCUSSION

- SDHD mutations account for >50% of hereditary head and neck paragangliomas, however, malignancy is found in less than 3% of these cases.
- Contrast CT and MRI are preferred initial imaging .
- Head and neck PGL are mostly non-secretory (95%), however, 3-methoxytyramine is a new marker that has been found to be elevated in one-third of head and neck PGL.
- SDHD mutations are transmitted in an autosomal dominant pattern and show a “parent-of-origin” inheritance, with disease manifestation occurring almost exclusively with paternally-transmitted mutations.
- Patients with SDHD mutation have a 75% risk of developing HNPGL during the life.
- SDHD mutation also predisposes to renal cell carcinoma and pituitary adenoma.

CONCLUSIONS

- The presence of multifocal paraganglioma raises suspicion for a genetic syndrome.
- PET CT or other functional imaging must be performed in all cases of paraganglioma to exclude metastatic disease. Concurrent thoraco-abdominal paragangliomas are present in 10-15% cases of SDHD related HNPGLs.
- Surgical resection is first line but may not be possible due to the location of the tumor
- Genetic evaluation must be pursued in all patients to predict risk of recurrent/metastatic disease.

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A case of synchronous medullary and papillary thyroid carcinomas in a patient with primary hyperaldosteronism

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INTRODUCTION

Synchronous presentation of medullary thyroid cancer (MTC), papillary thyroid cancer (PTC), and primary hyperaldosteronism (PA) has not been described. We present this case for its rarity and the uncertainty surrounding its etiology and course.

CASE DESCRIPTION

59 year old man post left adrenalectomy (unknown reason) and history of hypertension and hypokalemia was noted to have multiple thyroid nodules on a CT of chest.

- Thyroid U/S
  Right lobe: Multiple solid hypoechoic nodules, largest measuring 3.2 x 2.4 x 2.4 cm
  Left Lobe: Multiple solid and cystic nodules, largest measuring 1.1 x 1.0 x 1.0 cm
- FNA of the right largest nodule: concerning for MTC
- Endocrine labs:
  Calcitonin 13648 pg/mL (0-8.4)
  Carcinoembryonic antigen (CEA) 21.8 ng/mL (0-7)
  Aldosterone 128.1 ng/dL (0-30)
  Renin < 0.1 ng/dL (0.167-5.380)
  Plasma metanephrines ruled out pheochromocytoma
- CT chest/abdomen/pelvis: Right 1.1 cm adrenal nodule

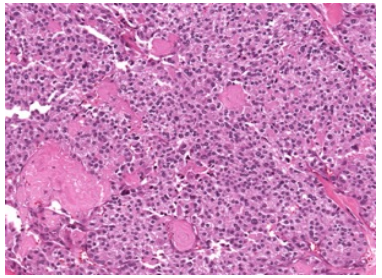
He underwent total thyroidectomy/selective neck dissection.

- Thyroidectomy specimen revealed a 3.8 cm right MTC and a 0.9 cm left PTC.
- 12/53 lymph nodes were positive for metastases from MTC; 2/53 were positive for both MTC and PTC.
- RET mutation negative

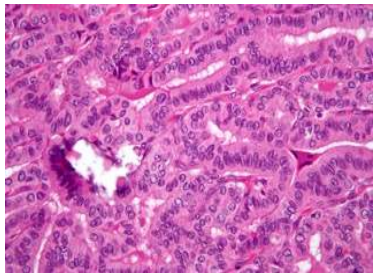
4 months postoperative follow up

- CEA and calcitonin levels trended down. Calcitonin-72.5 pg/mL and CEA-1.3 ng/mL.
- Thyroglobulin and thyroglobulin Abs - undetectable
- Persistently elevated aldosterone and renin levels consistent with PA.
- He was started on eplerenone.

FIGURES: HISTOPATHOLOGY



Solid lobular growth pattern and round polygonal tumor cells – Medullary thyroid cancer



Fibrovascular core with malignant epithelial cells on the periphery and cells with characteristic empty-appearing nuclei – Papillary thyroid cancer

DISCUSSION

- There is statistically significant increased incidence of US thyroid abnormalities in patients with PA.
- An imbalance between growth factors or cytokines may contribute to thyroid neoplasms development. The incidence of PTC in PA is ~1-4%.
- The relationship between thyroid carcinomas and PA subtypes (idiopathic vs. aldosterone producing adenoma) is unclear.
- The prevalence of PA in patients with PTC is 18.5%.
- Plasma aldosterone levels in PA patients with malignancy are higher than in patients without malignancy.

CONCLUSION

- This is the first described case of MTC in association with PA.
- The etiology predisposing malignant transformation of the thyroid in PA and the effect of high aldosterone levels in the course of cancer are yet to be elucidated.

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MON-328: Twenty years follow up of a patient with a novel MEN1 gene mutation

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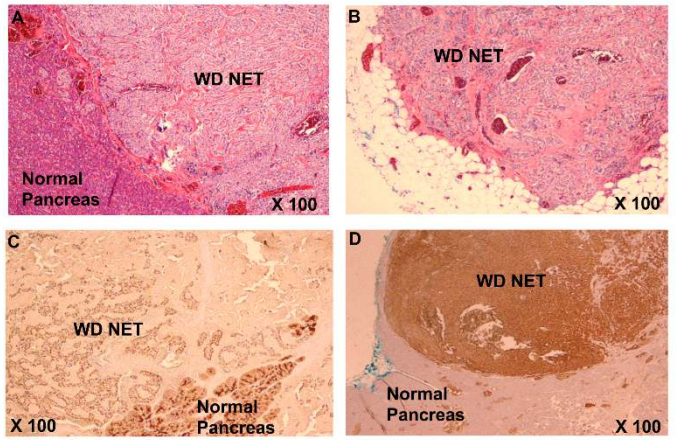
INTRODUCTION

- The multiple endocrine neoplasia type 1 (MEN1) syndrome is a rare autosomal dominant inherited tumor syndrome.
- Mutations in the MEN1 gene are detectable in approximately 70-90% of kindreds with classic MEN1 syndrome (1).

CASE PRESENTATION

- A 41 year old Caucasian male with a diagnosis of MEN1 syndrome has been followed up in our clinic for 20 years.
- At the age of 21, he had two parathyroid glands resection for hypercalcemia which revealed an adenoma of the right superior parathyroid gland. He had one more parathyroid gland resected 6 months later for persistent hypercalcemia.
- At the age of 33, he underwent total parathyroidectomy, thymectomy, and auto transplantation of half parathyroid gland in the left forearm for recurrent hypercalcemia.
- At the age of 39, he developed frequent hypoglycemic episodes with symptoms including confusion. Serum glucose levels of 20-30 mg/dL were documented during the episodes.
- A 72 hours fasting test showed a plasma glucose level of 53 mg/dL, with insulin level of 25.6 mU/L, proinsulin level of 5.2 pmol/L, C-peptide level of 5 ng/mL and low beta- hydroxybutyrate level. In response to 1 mg glucagon intravenous injection, plasma glucose level improved by 83 mg/dL in 30 minutes.
- He then had selective arterial calcium stimulation test and the results showed the insulin peak rising after stimulation in the splenic artery suggested that the lesion was in the body and tail of the pancreas (see Table).
- He had partial pancreatectomy and the pathology showed 4 foci of identical neuroendocrine tumors (see Figure).



Hematoxylin and eosin staining (A) and its invasion into peri- pancreatic fat (B). By immunohistochemical staining with pan-cytokeratin (C) and chromogranin (D). WD NET: well-differentiated neuroendocrine tumor.

Artery site	Basal	+30 min	+60 min	+90 min	+120 min	+180 min
Superior mesenteric						
Insulin (mU/L)	15.1	5.7	14.5	15.9	17.5	32.5
C-Peptide (ng/mL)	5.2	4.7	4.6	4.8	5.4	6.0
Gastro-duodenal						
Insulin (mU/L)	26.3	38.6	32.1	27.5	27.4	35.5
C-peptide (ng/mL)	5.7	6.6	6.3	5.8	5.8	6.4
Splenic						
Insulin (mU/L)	N/A	65.0	154.5	153.7	195.2	68.7
C-Peptide (ng/mL)	N/A	10.9	20.1	9.9	12.8	7.3

- Notably, he had intermittent abdominal pain after food intake and chronic watery diarrhea 5-7 times a day before pancreatectomy, which resolved after the surgery. The serum tests also supported a diagnosis of VIPoma: the VIP levels were 96.3 pg/mL preoperatively and 65 pg/mL postoperatively.
- The patient underwent genetic screening for MEN1 mutations which revealed the presence of a novel germline deletion mutation in exon 8 (1078delC), resulting in frame shifting of its coded menin protein (Arg360fsX13).
- The mutation occurred in the exon 8, which is critical for the major structure of menin (2). In the same codon 360, the mutation of c.1080ins12 causing frame shifting has been reported as a likely causal mutation of MEN1 syndrome. Therefore, most likely this deletion mutation represents the disease- causing mutation.

CONCLUSIONS

- This case revealed a novel MEN1 gene mutation in a patient with a rare pancreatic neuroendocrine tumor.
- The existence of a pancreatic neuroendocrine tumor co-producing insulin and vasoactive intestinal polypeptide in MEN1 patients has not been reported previously.
- The existence of a pancreatic neuroendocrine tumor co-producing insulin and vasoactive intestinal polypeptide in this patient might be a characteristic feature of this novel MEN1 gene mutation.

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SAT-095: The impact of treating OSA with CPAP on intensive calorie restriction- induced weight loss

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*The authors have nothing to disclose.

INTRODUCTION

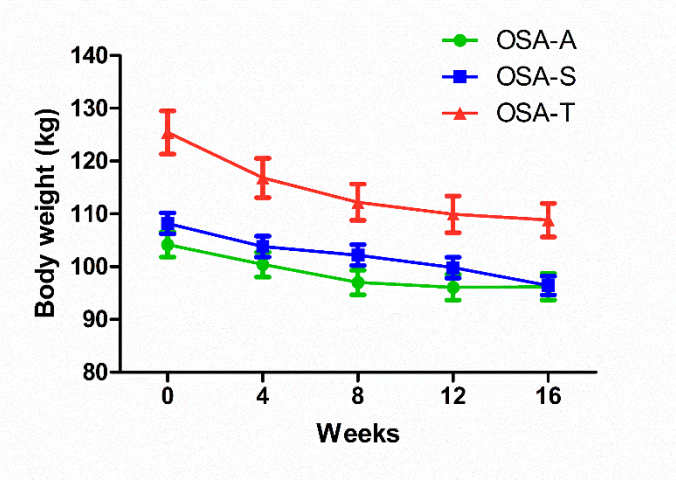
- Obesity has been recognized as a worldwide pandemic, and the first-line treatment is weight loss via a calorie restricted diet (1).
- Obstructive sleep apnea (OSA) is one of the key obesity-related comorbidities and has complex interactions with obesity and weight loss treatments.
- The impact of treating OSA with continuous positive airway pressure (CPAP) on calorie restriction- induced weight loss remains unclear.

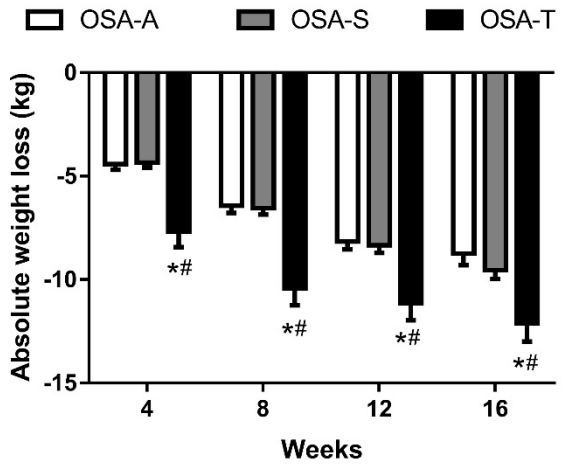
METHODS

- We conducted a pilot retrospective study with the patients seen in UAMS weight loss clinic from 1/1/2014 to 8/31/2017.
- Patients were eligible if they were 18-65 years old, body mass index >= 30 and < 50, and underwent a 16-week intensive calorie restriction weight loss program obtained by strict calorie restriction (800 Kcal per day), exercise programs, weekly individual counseling and cognitive behavioral therapy.
- Patients who suffered from thyroid dysfunction, uncontrolled diabetes, active infection, active malignancy, or end-organ damage were excluded.
- Participants underwent a standardized medical examination before and every week in the program.

RESULTS

- Of the 300 patients included in the analysis, the average ages was 55 ± 10 years old, and 236 (78.7%) were female.
- They were divided into three groups based on self- reported OSA symptoms and CPAP treatment status: asymptomatic OSA group (OSA-A, n = 89), symptomatic group (OSA-S, n = 164), and OSA on CPAP treatment group (OSA-T, n = 47).
- In 16 weeks, the absolute weight loss of the OSA-T group was significantly higher than that of the OSA-S and OSA-A groups (-12.1 ± 5.9 vs. -9.5 ± 5.5 vs. -8.7 ± 5.3 kg, $P < 0.01$), whereas, the percentage weight loss of the OSA-T group was not significantly higher than that of the OSA-A and OSA-S groups (-10.46 ± 5.63% vs. -9.14 ± 4.89% vs. -8.47 ± 4.97%, $P = 0.065$). There had no difference of the absolute weight loss between OSA-A group and OSA-S group.
- Further analysis established a correlation of CPAP treatment to the absolute weight loss after adjustment of baseline body weight, age and gender.





CONCLUSION

- Our results showed that the patients who had CPAP treatment achieved a larger weight reduction than non-CPAP treatment patients in a 16-week intensive calorie restriction weight loss program.
- Sleep quality may impact success in weight loss programs and several mechanisms may underpin this.
- The combination of weight loss and CPAP treatment should be considered for all obese patients with OSA.

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An unusual case of metastatic follicular thyroid cancer 40 years after initial diagnosis

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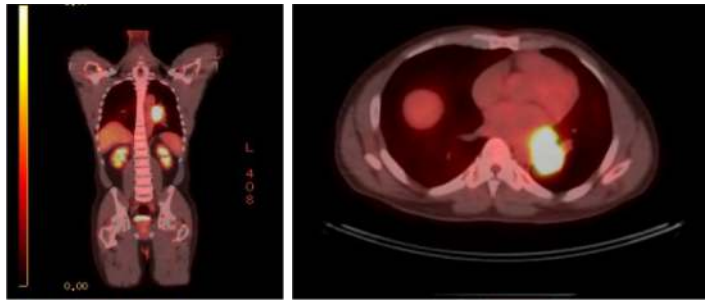
CASE PRESENTATION

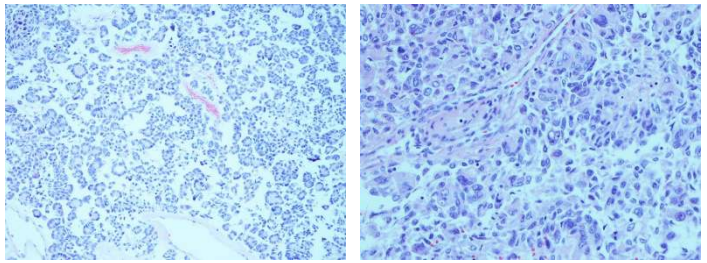
- 63 year old man with history of follicular thyroid cancer
- Post Total thyroidectomy in 1977 and radioactive iodine therapy (30 mCi) in 1978
- He had excellent response to therapy given:
  - Repeated normal neck US
  - Undetectable thyroglobulin (Tg) levels and negative Tg antibodies
  - negative Whole body scans in 1984, 2002 and 2010
- He was discharged from endocrine clinic in 2014.
- Presented in 2017 with new onset of wheezing on exertion.

INVESTIGATIONS

- Chest x-ray -> indeterminate left paraspinal/periaortic mass.
- CT chest -> 5.3 cm x 3.7 cm x 5.4 cm left hilar and infrahilar mass occluding the left lower lobe bronchus.
- Bronchoscopy with endo-bronchial ultrasound and transbronchial lymph node aspiration -> Cytology revealed metastatic follicular thyroid cancer. The tumor cells : positive for thyroid transcription factor-1, cytokeratin 7 and focally positive for Tg.
- Neck ultrasound -> no evidence of local recurrence.

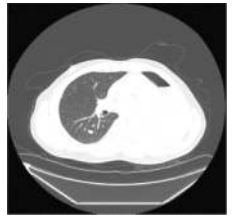


- PET/CT -> 3.9 cm x 3.7 cm x 5.2 cm FDG avid left lower lobe mass and subcentimeter, non FDG avid bibasilar parenchymal and subpleural nodules.
- Tg level remained undetectable.
- Left pneumonectomy and mediastinal lymphadenectomy was performed.



- Figure A: well differentiated thyroid cancer with thyroglobulin. Figure B: poorly differentiated thyroid cancer

- Final pathology
  - metastatic thyroid cancer consisting of a mixture of well-differentiated follicular cancer (70%, figure A) and anaplastic cancer component (30%, figure B).
  - Perineural /angiolymphatic invasion. The anaplastic component was associated with extensive intra-tumoral necrosis.
  - lymph nodes: 9/9 were negative for malignancy.
- Pathology was reviewed by a second institution -> no overt anaplasia was present and the tumor represents poorly differentiated thyroid carcinoma arising in a background of well differentiated follicular thyroid carcinoma.
- This was confirmed by another national referral center
- Post-op scans -> minimal increase in volume of right lower lobe nodule.



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- Referred to oncology -> treated with two cycles of doxorubicin and docetaxel.
- Further chemotherapy was held due to reduction in ejection fraction.
- Repeat scan in 3 months -> stable lung nodule with interval development of a new 4 mm nodule.
- RAI was unable to be performed due to frequent administration of IV contrast.
- He is currently under close active surveillance

DISCUSSION

- This case of metastatic follicular thyroid Ca 40 years after initial diagnosis highlights
  - Importance of counseling patients of the unlikely situation of late recurrence and identification of potential red flags prompting early follow up (e.g. shortness of breath).
  - limitations of Tg levels in following thyroid Ca.
  - Unusual fact of undetectable Tg levels despite the tumor staining positive for Tg.
- Our hypothesis: The metastatic follicular Ca was present in the lung for a long time before undergoing anaplastic transformation.
- It is unclear to us whether the metastasis was present but not detected at the WBS in 2010.

CONCLUSIONS

- The ideal time period for which patients with differentiated thyroid cancer should be followed for recurrence is unknown; metastasis may occur decades from the initial presentation.
- Physicians should be aware of the limitations of thyroglobulin levels in evaluating for recurrence/metastasis.

Atypical Subtrochanteric Fractures-Hypophosphatasia Under-recognized Disease

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INTRODUCTION

- Studies have shown that hypophosphatasia is frequently under-recognized in clinical settings.
- Atypical subtrochanteric femoral fracture is a described side effect of Bisphosphonate (BPP) therapy.
- There have been cases of atypical subtrochanteric femoral fracture in adult hypophosphatasia after exposure to BPP therapy.
- This brings up the possibility that some of the cases of atypical subtrochanteric femoral fracture after BPP are in fact unrecognized cases of hypophosphatasia.

CASE PRESENTATION

- 76-year-old woman with past medical history of HTN, several fractures and multiple therapies for Osteoporosis was referred to our clinic for management of Osteoporosis.

PRIOR ANTI-OSTEOPOROTIC THERAPIES

- 2000 -> Alendronate -> 4 years.
- 2004 -> Teriparatide -> 1 year.
- 2005 -> Alendronate -> 3 years.
- 2008 -> Zoledronic acid -> 1st infusion.
- 2009 -> Zoledronic acid -> 2nd infusion.
- 2010 -> Zoledronic acid -> 3rd infusion.
- 2015 -> Denosumab -> only received 1 dose.
- 2015 -> Teriparatide -> 1 year.
- 2016 -> Denosumab -> only received 1 dose.

PRIOR FRACTURE HISTORY

- 1996 -> Right wrist fracture.
- 1996 -> Right Patellar fracture.
- 2009 -> Bilateral femoral neck fracture status post internal fixation.
- 2011 -> Left foot metatarsal fracture.
- 2015 -> Atypical subtrochanteric femoral fracture (was attributed to BPP).
- 2016 -> Compression fracture of lumbar spine.
- 2017 -> Right foot metatarsal fracture.

RISK FACTORS

- Menopause at the age of 52 (estrogen therapy for 5 years).
- History of breast cancer, on Letrozole since 2009.

FAMILY HISTORY

- Osteoporosis, hip fracture, and several other pathological fractures in mother and both brothers.
- Patient has her own teeth, but one of her brothers lost all of his at the age of 18.

BMD RESULT

DexaScan Readings

Region	BMD	T-Score	Percentage	Z-Score	Percentage
Radial Diaphysis	.398	-4.9	57	-2.3	75
Ultradistal Radius	.252	-3.3	57	-1.4	76
Lumbar (PA) 1, 2, 4, 3	.717	-3	68	-.5	92
L3 (Lateral)	.616	-2.7	72	.7	111
Volumetric Lumbar (L3 in g/cm3)	.18	-2.7	72	.7	111
Femoral Neck					
Femoral Trochanter					
Total Proximal Femur					

- All regions were below the normal peak range. When compared with baseline studies done in 2008, there had been an increase of 8.2% at the radial diaphysis and a decrease of 5.6% and 10.4% at the posteroanterior and lateral lumbar spine.

LAB RESULT

- Alkaline phosphatase: 14 IU/L (Ref. 32-91).
- 25 hydroxyvitamin D: 106 ng/ml (Ref. 30-100).
- Intact PTH: 105 pg/ml (Ref. 12-88).
- Calcium: 9.2 mg/dl (Ref. 8.6-10.2).
- Ionized calcium: 1.2 mmol/L (Ref. 1.15-1.33).
- Phosphorus: 4.7 mg/dl (Ref. 2.5-4.5).

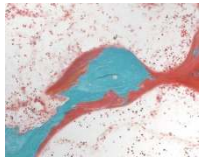
INVESTIGATION

- Bone alkaline phosphatase: 2.6 ug/L (Ref. postmenopausal: 7-22.4 ug/L).
- Vitamin B6:108 nmol/L (Ref. 20-125).
- Phosphophentholamine: 337 nmol/mgCr (Ref. <48).

=> Suggestive of adult hypophosphatasia.

DISCUSSION

- Hypophosphatasia is a rare heritable rickets or osteomalacia, which disturbs skeleton and teeth. Muscle weakness is often present.
- It is characterized by biochemically subnormal activity of tissue nonspecific isoenzyme of Alkaline phosphatase (TNSALP).
- BPPs are synthetic analogs of pyrophosphate which resist hydrolysis by Alkaline phosphatase and may have direct inhibitory effects on Alkaline phosphatase activity -> atypical subtrochanteric femoral fractures in adult hypophosphatasia.
- Labs in hypophosphatasia:
  - ✓ Alkaline phosphatase activity is below the age-matched normal range.
  - ✓ Accumulation of phosphoethanolamine (PEA), inorganic pyrophosphate (PPi) and pyridoxal 5'- phophate (PLP).
  - ✓ Hypercalcemia may be seen in infantile hypophosphatasia -> Could have suppressed PTH and 1,25 hydroxy vitamin D.
  - ✓ Hyperphosphatemia is seen in childhood and adult hypophosphatasia.



Extraordinary osteoid excess in hypophosphatasia: undecalcified cancellous bone. (The blue is mineralized bone and the red is osteoid).

CONCLUSION

- We present a case of unrecognized adult hypophosphatasia who was treated with BPP causing atypical subtrochanteric femoral fracture.
- We suggest that some cases of atypical subtrochanteric femoral fracture in the setting of BPP therapy could be unrecognized cases of hypophosphatasia, which may have a higher prevalence than initially thought. Obtaining a baseline Alkaline phosphatase prior to BPP therapy could be crucial.

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ALWAYS ACTED AS PARAGANGLIOMA, ALWAYS READ AS SCHWANNOMA

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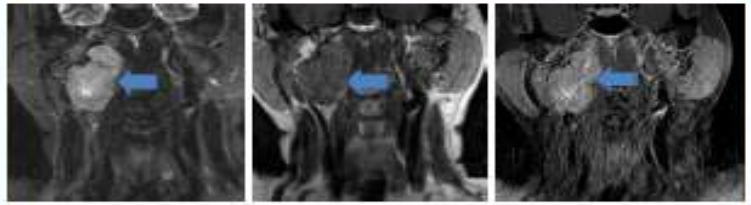
INTRODUCTION

- Head and neck paragangliomas (HNPGL) represent 0.6% of the head and neck tumors.
- Up to 95 % of HNPGL are non-secreting and up to 30% can be malignant.
- They often present as a cervical mass with compression or infiltration of adjacent structures or discovered on imaging.
- One of the differentials includes Schwannomas, which are rare benign tumors of nerve sheath origin that arise most commonly from the 8th cranial nerve.
- We present a case of secreting HNPGL, which was initially managed as a schwannoma.

CASE PRESENTATION

- 70-year old female, with history of uncontrolled hypertension, was diagnosed in 2010 with a right neck mass after presenting with ear pain.
- MRI showed a 3.2x3.1 cm mass in the right carotid space extending into the jugular foramen.

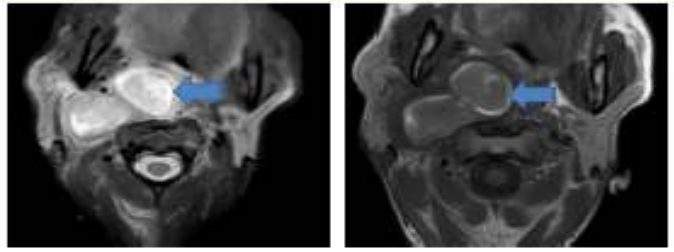
MRI 2010



Left: coronal T2,
Middle and Right: Pre and post contrast T1
Lobulated, enhancing, T2-hyperintense mass in the right neck along the carotid sheath

- Main differential diagnosis based on imaging was schwannoma vs paraganglioma. Post contrast enhancement on subsequent MRI was interpreted as characteristic of a schwannoma.
- A conservative approach was chosen and the mass remained stable until 2012.
- She was lost at follow up for 3 years, continued to have uncontrolled hypertension and developed systolic congestive heart failure.
- In 2015 she presented with sudden onset right side neck and ear pain and few months history of weight loss, dysphagia requiring PEG tube placement and dysphonia.
- Physical exam showed the palpable right neck mass and paralysis of the right 10th, 11th and 12th cranial nerves.
- Given the fact that the patient was clinically asymptomatic at presentation, but had developed several complications after five years repeat MRI was done which showed increase in size of the mass (6 cm), peripheral rim like enhancement and central necrosis with local compression.

MRI 2015



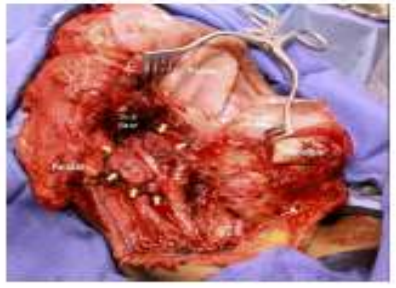
Axial T2 (left) and T1 (right) mixed signal within the central portion of the mass suggestive of intratumoral hemorrhage

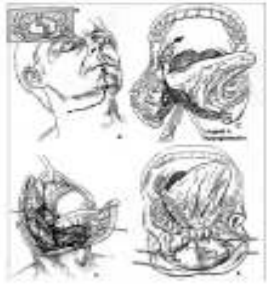
LABS

- Plasma Normetanephrine -> 2.42 nmol/l (ref. <0.89 nmol/l)
- Urine Normetanephrine -> 3258 ug/g Cr. (ref. <400 ug/g Cr)

SURGICAL APPROACH

- After preparation with phenoxybenzamine, the patient underwent partial resection of the mass. The intracranial portion was not removed.



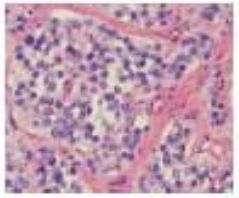


- Post-operative evaluation showed normal plasma and urine normetanephrines with stable intracranial lesion.
- The blood pressure control improved after the removal of the mass, but unfortunately dysphagia and dysphonia did not resolve.

PATHOLOGY

- Pathology was compatible with paraganglioma with extensive central infarction. No features of malignancy and no metastatic involvement of lymph nodes was present.

Medium power 100x – rounded nests of varying size in a zellballen pattern



High power 400x – mild pleomorphism of type I cells (chief cells)

Synaptophysin immunostaining

DISCUSSION

- Both schwannomas and paragangliomas have low signal on T1-weighted images and an intermediate to high signal on T2-weighted images.
- Clinical picture was thought to be more suggestive of paraganglioma, although imaging was interpreted as schwannoma, which prompted us to do the hormonal workup.
- HNPGL are associated with a significant risk of malignancy and require preoperative management.
- It is imperative to differentiate them from benign tumors based on clinical manifestation, biochemical testing (although mostly are non-secretory), and imaging characteristics.
- One could consider PET/CT-[18F]FDOPA with sensitivity of above 90% and specificity of above 95%, based on availability, when in doubt.

CONCLUSION

- We present a case of normetanephrine secreting head and neck paraganglioma, which was initially interpreted as schwannoma on imaging.
- This case highlights the limitations of diagnostic techniques in the differential diagnosis of the complex neurovascular lesions.

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