A syndromic red herring in a curable cancer

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Introduction

We present a 34 year old male with a complex and prolonged diagnostic pathway due to his family history of succinate dehydrogenase deficiency (SDHD). The patient has a heterozygous intragenic pathogenic *SDHD* variant: c.94_95delTC p.Ala33IlefsX35.

Genetics

Hereditary Head and Neck Paragangliomas (HNPGL) and Phaeochromocytoma and Paraganglioma (PPGLs) are most commonly caused by a pathogenic variant in one of the subunit genes (*SDHB/SDHC/SDHD*) of the succinate dehydrogenase (SDH) enzyme complex. HNPGLs and PPGLs are rare neuroendocrine tumours which arise in the head and neck, or the adrenal medulla, respectively.[1] Up to 40% of PPGL cases can be attributed to a germline variant in a susceptibility gene. The spectrum of tumours associated with *SDHx* variants extends to gastrointestinal tumours (GIST), renal cell carcinoma (RCC) and pituitary adenomas.[2]

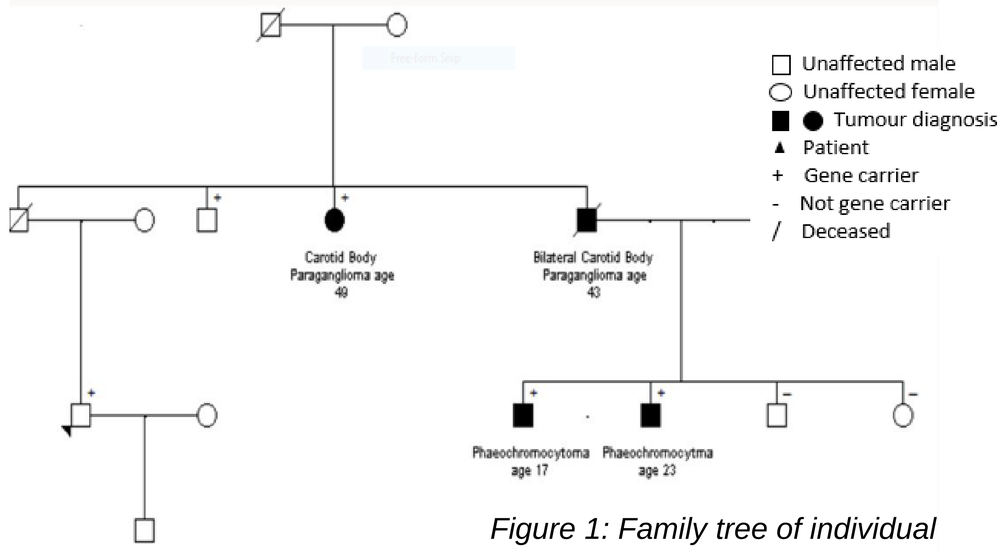


Figure 1: Family tree of individual

Presentation

Back pain, progressive bilateral lower limb weakness and acute urinary retention.

Found to have an enlarged testicle and history of a treated hydrocele.
AFP (alpha-fetoprotein) elevated at 17318 kU/L (0-6), Beta-HCG <3 U/L (0-5) and LDH 694 U/L (80-240).
US testis unremarkable but biopsy of the paravertebral mass confirmed a **non-seminomatous germ cell–yolk sac tumour.**

<u>CT chest, abdomen and pelvis</u> = 10 x 11 x 12cm right paravertebral mass originating from a moderately collapsed T11 vertebral body with additional lytic lesion within T10.
<u>MRI spine</u> = cord compression at T11.
Admitted under the neurosurgeons.
Due to his family history of SDHD, this was felt to represent an aorto-sympathetic paraganglioma

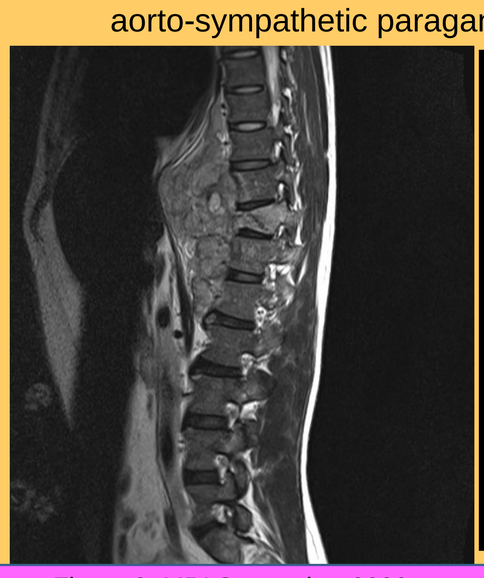


Figure 2: MRI September 2020

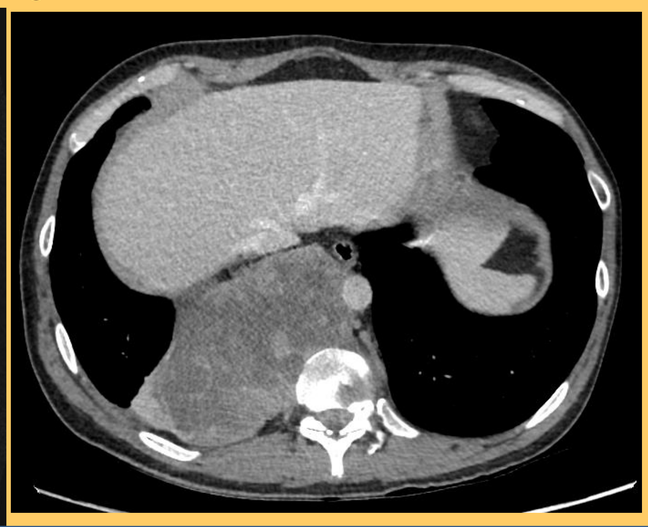


Figure 3: CT CAP September 2020

<u>Endocrinology review:</u>
Plasma/urine metanephrines and an <u>MIBG (iodine-123 meta-iodobenzylguanidine) scan</u> was suggested.
The mediastinal lymphadenopathy and large mass at the right lung showed no MIBG uptake, but the right supraclavicular mass showed abnormal uptake.
Plasma metadrenalines normal. CT biopsy postponed whilst started on alpha blockers.

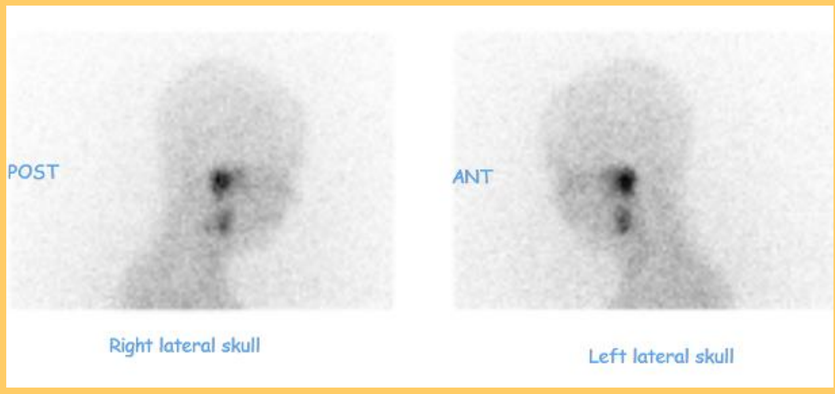


Figure 4: MIBG September 2020

September 2021

<u>Transfer to oncology</u>
Started CBOP BEP chemotherapy. [3]
AFP fell to 35 kU/L.
Wheelchair bound → walking with a zimmer frame.

Partial response to chemotherapy and a reduction in the size of all lesions.

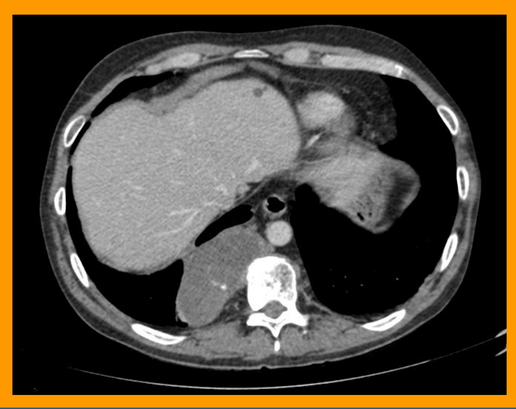


Figure 5: CT CAP November 2020

Chemo completed.
AFP 35 kU/L
End of treatment CT and MRI scans = response but still diffuse residual disease.
Not amenable to surgery.

December 2020

Due to several reasons (COVID 19-pandemic, bony involvement and presumed metastases) consolidation radiotherapy was delivered (30 gray in 10 fractions) to the retroperitoneal mass.

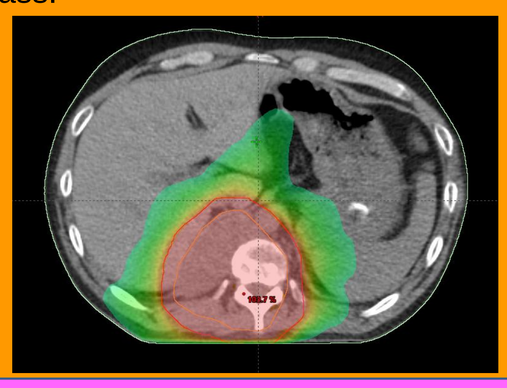


Figure 6: Radiotherapy plan March 2021

Recurrence of night sweats, fatigue and SOBOE.
AFP risen to 13 kU/L.
MRI = paraspinal disease was involuting after radiotherapy.
AFP continued to rise to 23 kU/L but as good quality of life, chemo was deferred.

October 2022

AFP 149 kU/L and commenced on TIP (Paclitaxel, Ifosfamide and Cisplatin) chemotherapy.

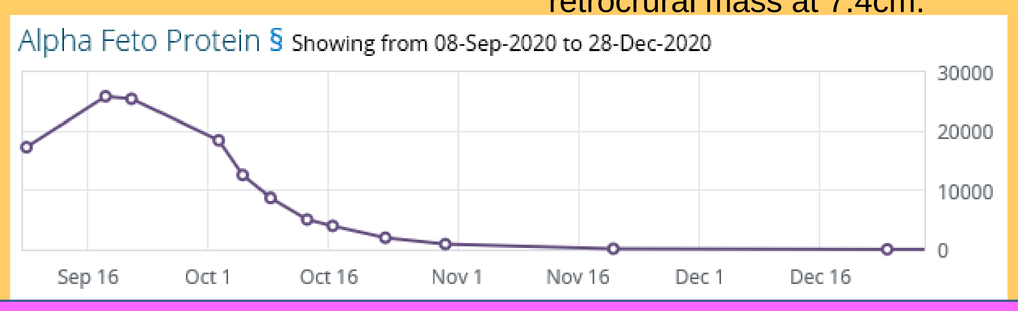


Figure 7: Alpha-fetoprotein graph

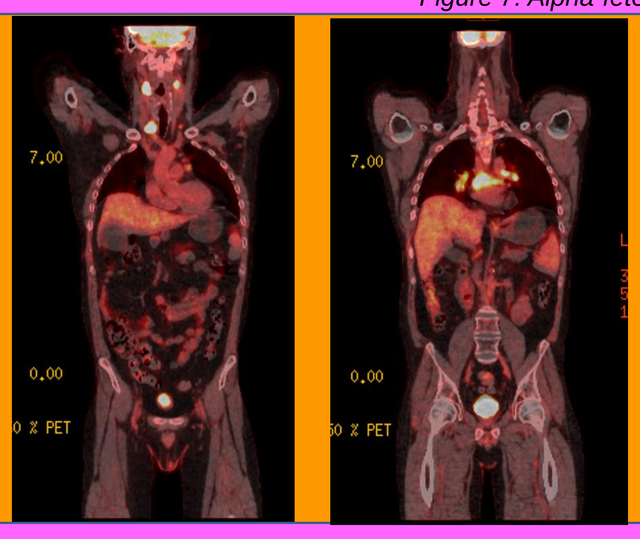
Following his final cycle, AFP had dropped to 4kU/L.
CT showed stable disease with a right retrocrural mass at 7.4cm.

PET November 2022

Resection of residual masses (mediastinal nodes, retrocrural paravertebral mass and retroperitoneal lymph node).
Pathology confirmed differentiated teratoma.
The retrocrural mass showed extensive necrosis with no viable tumour. AFP post operatively returned to normal.

February 2022

Repeat CT showed mediastinal nodes, left paratracheal node and subcarinal node had all increased in size and he had a new right hilar lymph node.
Markers all normal.



Due to his SDHD mutation and complex history, a PET scan was requested. The paraphrayngeal, supraclavicular and right para adrenal regions were consistent with paraganglioma but the hilar, mediastinal and left supraclavicular nodes were more consistent with metastatic germ cell tumour. Due to the wide differential, a biopsy of the subcarinal node was organised via mediastinoscopy.

Interestingly, pathology has come back with a non caseating granuloma, in keeping with sarcoid.
He has subsequently been referred to Respiratory for this 3rd diagnosis.

January 2023

Conclusion

This case highlights the importance of a widened differential diagnosis. In a young male with a paravertebral mass, tumour markers should always be included in the work-up and germ cell cancer should be excluded.

References:
1) Cornu E, Belmihoub I, Burnichon N. et al. Phéochromocytome et paragangliome. La Revue de Médecine Interne. 2019;40(11):733-741
2) MacFarlane, J., Seong, K., Bisambar, C. et al, 2020. A review of the tumour spectrum of germline succinate dehydrogenase gene mutations: Beyond phaeochromocytoma and paraganglioma. *Clinical Endocrinology*, 93(5), pp.528-538.
3) Huddart, R., Gabe, R., Cafferty, F. et al 2015. A Randomised Phase 2 Trial of Intensive Induction Chemotherapy (CBOP/BEP) and Standard BEP in Poor-prognosis Germ Cell Tumours (MRC TE23, CRUK 05/014, ISRCTN 53643604). *European Urology*, 67(3), pp.534-543.