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A complex case of three primary malignancies associated with a germline *SMARCB1* pathogenic variant

Judith A Eelloo [1], Miriam J Smith [1,2], Naomi L Bowers [1], John Ealing [1,3], Paul Hulse [4], James P Wylie [5], Patrick Shenjere [6], Noel W Clarke [7], Calvin Soh [8], Richard W Whitehouse [8], Mark Jones[9], Christopher Duff [10], Anthony Freemont [11], D Gareth Evans [1,2]

1. Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University Hospitals Foundation Trust, Manchester, UK

2. Division of Evolution and Genomic Sciences, School of Biological Sciences, University of Manchester, Manchester, UK

3. Department of Neurology, Salford Royal Foundation Trust, Manchester, UK

4. Department of Radiology, 5. Departments of Medical Oncology, 6. Department of Histopathology, 7. Department of Clinical Urology, The Christie NHS Foundation Trust, Manchester UK

8. Department Radiology, Manchester Royal Infirmary, Manchester University Hospitals Foundation Trust, Manchester, UK

9. Department of Cardiothoracic Surgery, 10. Department of Plastic Surgery, Wythenshawe Hospital, Manchester Universities Foundation Trust, Manchester, UK

11. Department of Histopathology, Manchester Royal Infirmary, Manchester Universities Foundation Trust, Manchester, UK

Correspondence: Judith Eelloo, Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester M13 9WL Email: judith.eelloo @mft.nhs.uk

Tel: +44 (0)161 276 6506; Fax: +44 (0)161 276 6145

Abstract

A 51-year old woman presented with a 6-month history of increasing pelvic/lower back pain with nocturnal waking and episodes of anorexia and vomiting. She had been given the diagnosis of Neurofibromatosis Type-1 25-years previously following removal of an intradural extramedullary schwannoma.

Examination revealed right torticollis and Horner's syndrome, a large abdominal mass arising from the pelvis, but no cutaneous stigmata of Neurofibromatosis Type-1. Magnetic resonance and positron emission tomography imaging revealed A) a 14cm heterogeneous enhancing mass, abutting the left kidney with standardised uptake value max=2.9, B) a large heterogeneous enhancing pelvic mass C) mesenteric adenopathy standardised uptake value max=10.3 and D) 6cm right lung apex mass standardised uptake value max=4.3.

Computerised tomography-guided biopsy of lesion A was reported as neurofibroma with occasional atypia, lesion B a benign uterine leiomyoma and lesion C follicular Lymphoma world health organisation Grade 2.

Genetic analysis of blood lymphocyte DNA identified a pathogenic variant in *SMARCB1*.

Following multidisciplinary discussions with genetic, oncology and surgical input it was decided that the lymphoma treatment should take priority. However, excision of the retro peritoneal mass was recommended due to the risk of malignant change.

Following 6-months chemotherapy for lymphoma, surgery was performed. Histology revealed a malignant peripheral nerve sheath tumour with areas of low and high-grade change. An incidental, well-differentiated small bowel neuroendocrine carcinoma was also excised. Close surveillance continues with no recurrence after 5 years. This raises new considerations for malignancy associated with *SMARCB1* pathogenic variants and highlights the importance of holistic, specialist and multidisciplinary care.

Keywords: Schwannomatosis; Neurofibromatosis type 1; Neurofibromatosis type 2; Malignancy; *SMARCB1*; Follicular lymphoma; MPNST

Case report:

A 51 year old woman rang the Nerve Tumours UK (helpline for advice formally The Neuro Foundation, a UK based charity for Neurofibromatosis). She had been diagnosed with Neurofibromatosis type 1 (NF1) aged 26-years following removal of a benign tumour from her spine. She had recently been investigated by her local gynaecology team for fibroids and had been informed that a computerised tomography (CT) scan had revealed a 14cm mass in her retro peritoneum. The gynaecologist referred her back to her GP recommending a referral to a neurologist in case it was related to her diagnosis of NF1. Being a nurse herself, she wanted to be proactive in this referral and sought advice. The Nerve Tumours UK specialist advisor suggested she make contact with one of the Nationally Commissioned specialist services for complex NF1 based at St Mary's hospital Manchester. Her call was triaged by a nurse specialist and she was assessed urgently in the complex NF1 clinic four days later.

Her detailed previous medical history was taken. A right latero and retro Collis with a dystonic tremor had been present since her teens. She had acquired a diagnosis of NF1 aged 26. This was following an L1 decompressive laminectomy and removal of an intradural extra medullary tumour in 1986 following a 2-year history of hip and back pain. This was histologically reported as a schwannoma; however, she was told she had NF1. In 1996 a painful lump was removed from the base of her finger, reported histologically to be an angioleiomyoma and a further painful 6mm schwannoma was removed from the left transverse cervical nerve in 2000. In 2011, a routine review at her local opticians had detected that her right pupil was not dilating so had referred her for an ophthalmology assessment where the presence of a

Horner's syndrome was confirmed which had been present for an indeterminate time. She was referred for Magnetic Resonance Imaging (MRI) of her head and neck where it was reported that she had two neurofibromas in her neck causing the Horner's syndrome and she was discharged. She reported that she had always been fit and well until 6-months previously when she had developed increasing pelvic and lower back pain that had woken her at night. This had been controlled by taking paracetamol and codeine. Other symptoms had included episodes of anorexia and vomiting resulting in some weight loss, and episodes of menorrhagia. Her GP had therefore referred her for gynaecological assessment. Pelvic scan revealed cervical and uterine fibroids but also a 14cm tumour in her left retro peritoneum.

On questioning she revealed no problems during childhood with schooling, learning or behaviour and had been good at sport.

Family history was taken and revealed that she had no biological children. She had 3 siblings consisting of 1 brother, who had died aged 4 from acute lymphoblastic leukaemia, 2 sisters and 8 nieces and nephews who had no relevant medical history. Her mother had died aged 33 years of a brain tumour which she had presumed to be NF1 related. Her maternal grandmother died of a stroke in her 70's but was also known to have had a tumour in her neck and spine removed. No histology was available.

Full neurological examination revealed a tall slim woman with a noted right retro and latero collis and a right Horner's syndrome. A fine tremor was noted in her arms but normal tone, power, reflexes and co-ordination was recorded. There was some sensory loss in the left ring finger due to previous excision of angioleiomyoma. A palpable mass was present in the left flank and a large central mass palpated under the umbilicus arising from the pelvis. Detailed skin examination with a woods lamp

revealed no abnormal pigmentation or cutaneous stigmata of NF1; no café au lait patches, inguinal or axillary freckling or Neurofibromatosis type-2 (NF2) plaques. No Lisch nodules were present on examination of the iris with a slit lamp. There were several soft non-painful lumps on the fingers and left side of neck. At this point with no cutaneous lesions plus histological confirmation of 2 schwannomas, the previously held diagnosis of NF1 was discounted and informed consent was taken for *NF2* and Schwannomatosis genetic testing.

Urgent MRI Imaging was performed in December 2011. This revealed normal cranial imaging. Pelvic and whole spine imaging showed a vertebral haemangioma at L3 and several small enhancing intradural lesions at T8-T12 and L1. There were also 4 significant retroperitoneal lesions . This was followed up with positron emission tomography (PET) imaging. This revealed A) a 14cm heterogeneous enhancing mass, abutting the left kidney with standardised uptake value max (SUV max) =2.9, B) a large heterogeneous enhancing pelvic mass C) mesenteric adenopathy SUV max=10.3 and D) a 6cm right lung apex mass SUV max=4.3.

Computerised tomography-guided biopsy of lesion A was reported as neurofibroma with occasional atypia, lesion B a benign uterine leiomyoma and lesion C follicular Lymphoma world health organisation Grade 2. Images are shown in Figures 1 and 2.

Following multi-disciplinary team discussion plan of care was as follows;

1) Follicular lymphoma was treated first as it showed high intensity on PET scan, higher than typically expected for low grade lymphoma- 8 cycles of R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone)

2) Abdominal surgery for removal of the retroperitoneal mass was undertaken following lymphoma treatment as the tumour was thought to have significant malignant potential (15-30%) even though biopsy was negative as the tumour was so large and had grown substantially in the interim (14cm cranio caudal length at MRI 16/12/11 and 19cm on excision 26/11/12). Surgery was performed and a retro peritoneal tumour size 190x157x126 mm. 1920g was removed. Histology from the tumour revealed that it was a malignant peripheral nerve sheath tumour (Figures 3&4). The left kidney was also removed and a 3cm well differentiated neuroendocrine carcinoma was identified and removed from the mid jejunum. No adjuvant therapy was given.

3) At a later date, following growth detected on serial imaging, a benign schwannoma (7.3x6.4) was removed from the right lung apex.

Surveillance imaging continues with no recurrence following 5 years.

Genetic Studies:

Genetic analysis of blood lymphocyte DNA was negative for *NF2* pathogenic variants. However, a frameshift, truncating variant, c.38delA, was found in *SMARCB1* exon 1, confirming a diagnosis of schwannomatosis. Genetic testing for other family members was offered.

This case represents the fourth case out of 75 *SMARCB1* pathogenic variant related schwannomatosis affected individuals with malignant peripheral nerve sheath tumour (MPNST) on the Manchester database of Manchester tested patients.

Discussion:

This case study describes a novel finding of three separate synchronous primary malignancies in a patient with Schwannomatosis and a proven *SMARCB1* pathogenic variant.

Schwannomatosis is a tumour predisposition syndrome currently characterized by the presence of two or more non-intradermal schwannomas, (benign peripheral nerve sheath tumours), with at least one with histologic confirmation and no evidence of vestibular tumour on high quality MRI scan and no known constitutional *NF2* pathogenic variants in a subject over 30-years (1). In 2007 *SMARCB1* was recognised as a causative gene for schwannomatosis (2). *SMARCB1* is a gene located on 22q and is involved in chromatin remodelling. Pathogenic variants in the *SMARCB1* gene are known to be linked with two additional conditions: Coffin-Siris syndrome and rhabdoid tumour predisposition syndrome. Studies have shown *SMARCB1* as the underlying cause in 45% of familial cases and 9% of sporadic cases who fulfil diagnostic criteria for schwannomatosis (3)

Partial or whole gene deletion of *SMARCB1*, as well as truncating variants of the central exons, are common in Atypical Teratoid Rabdoid Tumours, while *SMARCB1* variants associated with schwannomatosis tend to be non-truncating(4). There have been reports of rare families with *SMARCB1* variants associated with both schwannomatosis and rhabdoid tumours (5-7). A woman with schwannomatosis and a leiomyoma of the cervix uteri has also been reported previously with a *SMARCB1* splice-site variant (8).

The variant associated with this case is a frameshift variant in exon 1, c38delA, which introduces a premature termination codon. This would be expected to cause nonsense-mediated decay of the resulting mRNA transcript; however, expression studies of this variant have demonstrated that it results in re-initiation of the transcript at a

downstream methionine codon (9). This reinitiated transcript is thought to be less stable than the full-length transcript, which may account for the severe phenotype seen in this patient.

This case highlights that along with access to emerging specialist centres such as the nationally commissioned services for NF1 and NF2 in England, genetic testing will undoubtedly help with the mis-diagnosis of rare diseases. In this case an initial diagnosis of NF1 had been given some years earlier which of course would have predisposed the patient to a different set of clinical risks. Accurate histological confirmation from tumours is critical in achieving correct diagnosis, although hybrid tumours with histological and immunohistochemical features of both schwannoma and neurofibroma have been reported (10-12) and occur in both NF2 and schwannomatosis.

This case strongly supports the importance of specialist centres that provide expert holistic multidisciplinary care for complex and rare cases. There were 9 different disciplines involved in the careful planning of the most effective pathway for this patient. Had this not been available there could potentially have been a poorer outcome for this patient.

Malignancy is thought to occur rarely in schwannomatosis and has only become recognised more recently (7, 13-15). Whilst rhabdoid syndrome is associated with a highly malignant childhood tumour no clear adult pattern of malignancy has been established in the few survivors. Equally only a few hundred *SMARCB1* related schwannomatosis cases have been identified with an already established risk of

MPNST (14). This case not only highlights this consideration, but raises the possibility of perhaps a more extended malignancy phenotype associated with a *SMARCB1* pathogenic variant. Finally, this highlights the importance of holistic, specialist and multidisciplinary care in the assessment of tumour predisposition syndromes.

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Figure 1. The upper arrow indicates a 14cm solid heterogeneous enhancing tumour in the left retro peritoneum lying anterior to and compressing the lower pole of the left kidney, but with no extension into the spinal canal. PET showed intermediate intensity (SUV max 2.9). CT guided biopsy histology indicated features suggestive of peripheral nerve sheath tumour consistent with a neurofibroma and with no evidence of malignancy. The lower arrow indicates a large pelvic mass extending up to the aortic bifurcation with no activity on PET. CT guided biopsy histology indicated a benign uterine leiomyoma with areas of adenomyosis.
Mesenteric adenopathy PET showed high intensity (SUV max 10.30). CT guided biopsy histology indicated (WHO) grade 2 follicular lymphoma.

Figure 2: The arrow indicates a 6cm paravertebral tumour of the right lung apex, with intermediate PET-SUV intensity (max 4.3), which extends through the superior mediastinum, abutting the right side of the trachea, probably arising from sympathetic chain and showing no significant displacement.

Figure 3: MPNST (upper part of the image) arising on a back of a benign peripheral nerve sheath tumour/schwannoma (lower half of image)

Figure 4: a. MPNST with extensive tumour necrosis (right side of image); b. The tumour has brisk mitotic activity, with some atypical mitotic figures