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Multifocal neuromuscular hamartoma with smooth muscle and Schwannian components

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Accepted 13 August 2024

To cite: Atchison TJ, Ilyas F, Satturwar S, *et al*. *BMJ Case Rep* 2024;**17**:e256041. doi:10.1136/bcr-2023-256041

SUMMARY

A male in his early 20s with gastro-oesophageal reflux disease and severe weight loss was found to have two intrabdominal masses causing his symptoms: one in the gastro-oesophageal junction and the other occupying the coeliac plexus in the cardiophrenic region. These masses were surgically removed and sent to pathology where they were found to be smooth muscle hamartomas with Schwannian components. These represent a unique presentation of benign smooth muscle tumours that is not typically seen in young adults, especially in the cardiophrenic region involving the coeliac plexus.

BACKGROUND

A tumour with Schwannian components presenting in the anterior mediastinum is an exceedingly rare find. Tumours involving nerve cells in the mediastinum present almost exclusively in the posterior mediastinum. A patient with a tumour of this rarity with concurrent Marfanoid habitus is strongly suggestive of an underlying genetic component of unknown aetiology. To date, no literature has been published documenting a conclusive genetic syndrome with this symptomology. This patient's presentation is documented here along with the corresponding histopathology and genetic analysis, with the goal of adding to the current literature for the purpose of identifying similar patients and eventually shedding light on what may be the underlying cause of this patient's unique presentation.

CASE PRESENTATION

A male in his early 20s presented to the surgical oncology clinic for management of thoracic and intrabdominal soft tissue masses. He reported a 1-year history of persistent vomiting, gastro-oesophageal reflux disease (GERD), early satiety and abdominal cramping when eating. These symptoms were managed by his primary care physician with ondansetron 4 mg and pantoprazole 40 mg, which failed to control his symptoms. His symptoms continued to worsen and over the next several months he developed fatigue and a 25-pound unintentional weight loss. His other medical history included attention deficit hyperactivity disorder, pectus carinatum and marfanoid habitus with negative genetic testing for Marfan syndrome. His surgical history included an umbilical hernia repair 8 years prior. His family history was significant for breast cancer on his maternal side.

INVESTIGATIONS

An upper endoscopy was nondiagnostic. MRI imaging, seen in figure 1, revealed two masses: one located at the gastro-hepatic ligament involving the gastro-oesophageal junction, the other within the cardiophrenic region involving the coeliac axis. Fine needle aspiration biopsy of the masses demonstrated bland spindle cell proliferation showing patchy myxoid tissue with positive staining for desmin, *SOX10* and S-100. This cytology was suspicious for spindle cell neoplasm. On presentation at surgical oncology, his body mass index was 16.49 and his Eastern Cooperative Oncology Group performance status was 3.

DIFFERENTIAL DIAGNOSIS

Sudden, severe weight loss in a paediatric or young adult patient is most concerning for a mental health diagnosis, such as anorexia nervosa. In a patient with no changes in eating habits, a disorder of malabsorption, like inflammatory bowel disease, is a concern.[1–3] In a patient with accompanied nausea and vomiting, cyclic vomiting syndrome, bulimia nervosa and cannabinoid hyperemesis syndrome are all possible.[4–9] In a patient such as this, with nausea, vomiting and weight loss unexplained by a routine workup, a mechanical obstruction such as a gastric outlet or small bowel obstruction, should be considered.[10 11] This patient had an esophagogastroduodenoscopy evaluate for a mechanical obstruction, but it was inconclusive. A CT scan was performed to evaluate if there were any obvious structures compressing the patient's alimentary canal following the nondiagnostic EGD. This revealed the two tumours in the gastro-oesophageal and cardiophrenic region, and the CT was immediately followed by an MRI for better visualisation. Tumours in this region are concerning for cancers, such as lymphoma or extragonadal germ cell tumours.[12 13] However, given the lack of B-symptoms and the MRI showing clear compression of the gastrointestinal tract, a benign growth exhibiting a mass effect was more likely. A fine needle aspiration was performed to evaluate if the patient was a primarily surgical candidate or if they needed chemo/radiation before any procedure was performed. The biopsy showed spindle cells positive for desmin, S-100 and *SOX10* genes. Categories of spindle cell neoplasms include neurofibroma, fibroma, lipoma, leiomyoma and fibromatosis. The presence of *SOX10* and S-100 implied a nerve cell component to the tumour. The inclusion of desmin in the biopsy as well was highly unusual and implied a benign tumour of mixed nerve and

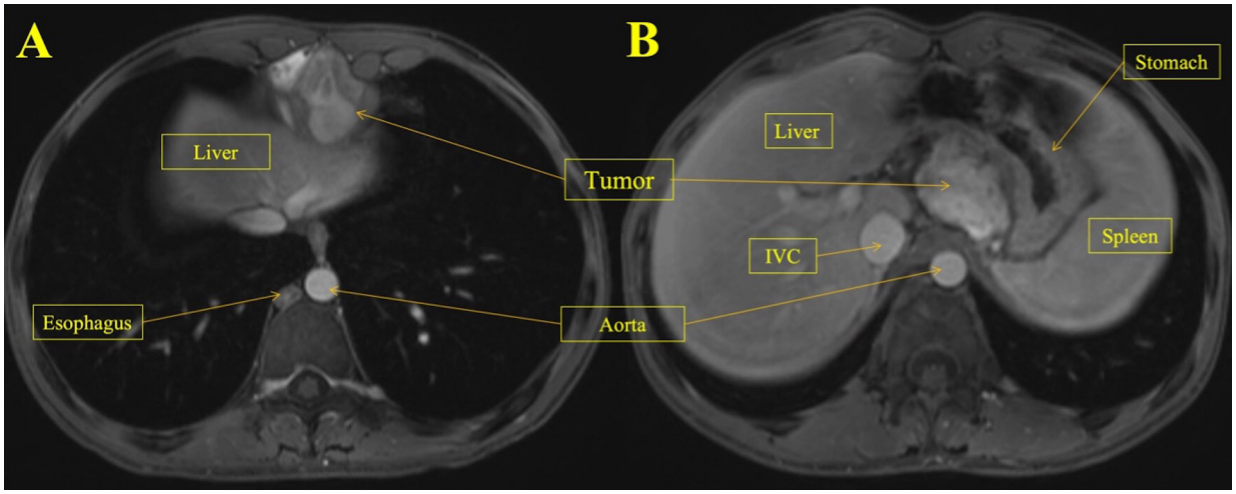

Figure 1 MRI imaging showed two heterogeneous, highly attenuated masses. The first (A), a midline mass within the cardiophrenic/retrosternal area extending into the abdomen and abutting the left lobe of the liver. The second (B), an intraabdominal mass located in the lesser sac, deep to the gastrohepatic ligament and impinging on the gastro-oesophageal junction near the spleen and inferior vena cava (IVC).

muscle aetiology causing a physical compression of the gastrointestinal tract due to mass effect without any signs of malignancy.

TREATMENT

Given these findings, surgical resection was recommended. After obtaining informed consent, the patient was taken to the operating room after a short period of nutritional optimisation. The surgery began with a midline incision from the xiphoid process to below the umbilicus. A solitary mass was identified at the lesser curvature of the stomach at the coeliac axis. The gastrohepatic ligament, with an aberrant left hepatic artery, was ligated to enter the lesser sac. The tumour was found to be adherent to

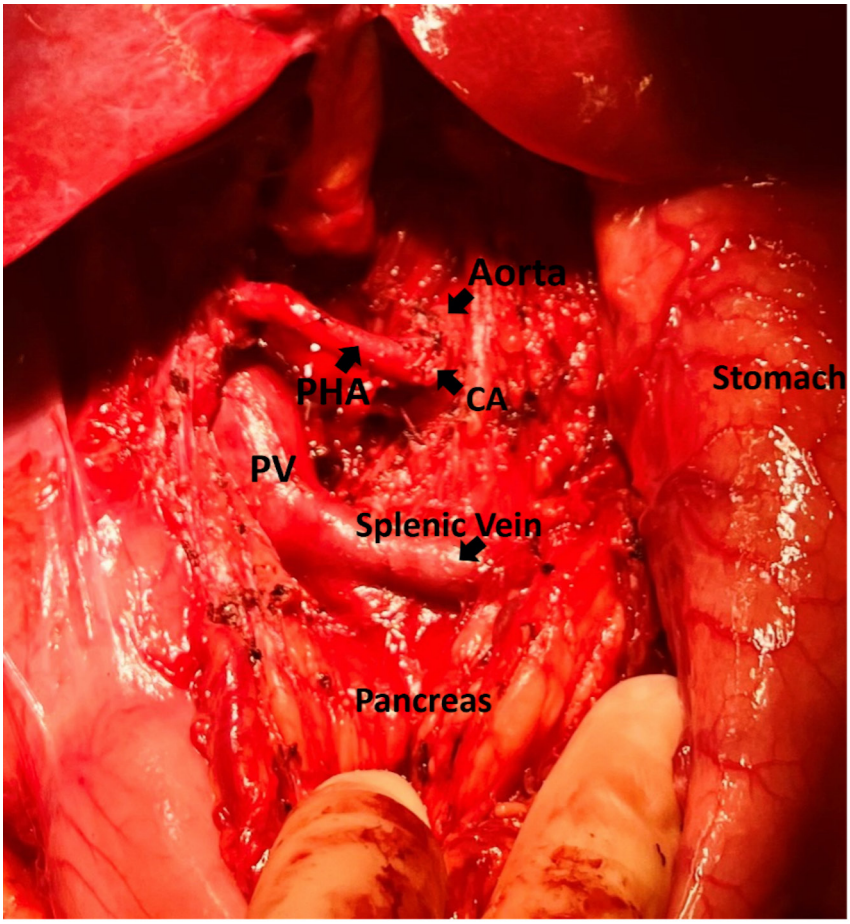

Figure 2 Dissection of the mass off of the aorta and the coeliac trunk required ligation of the splenic artery and left gastric artery, leaving just the proper hepatic artery (PHA) as it comes off the coeliac axis (CA). Portal vein, PV.

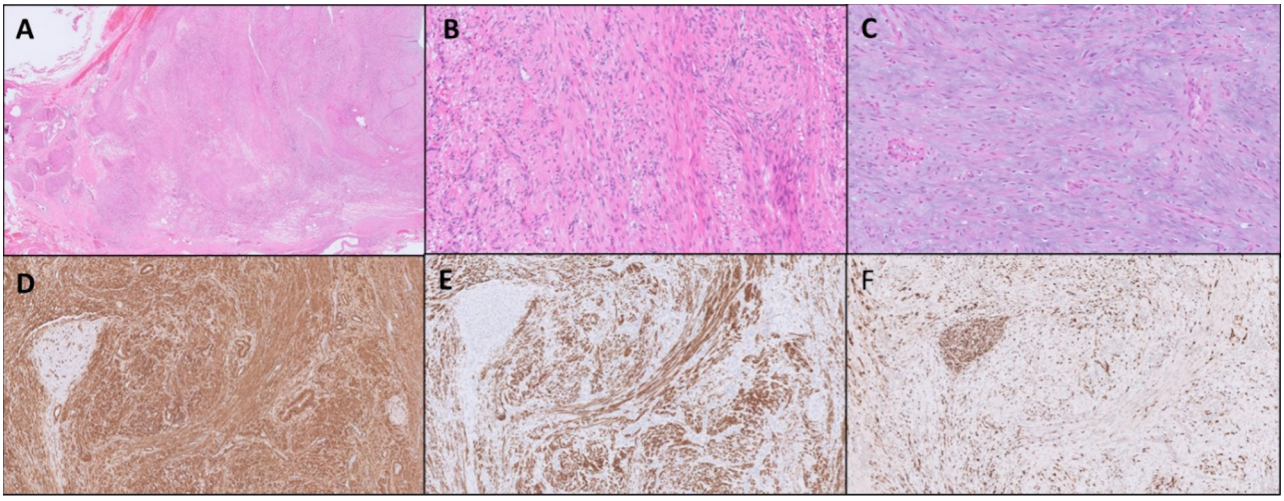

Figure 3 Histopathology and immunohistochemistry findings of a mesenchymal hamartoma with neuromuscular components. (A) Low magnification view showing proliferation of spindle cells and hyperplastic nerve bundles at the edge. (B) Higher magnification showing proliferation of bland spindle cells with eosinophilic cytoplasm, bland nuclei and inconspicuous nucleoli morphologically resembling fibroblastic cells. Note the absence of cytological atypia, necrosis or mitosis. (C) Variable myxoid change was present. (D,E) The fibroblastoid looking spindle cells were diffusely positive for smooth muscle markers SMA and desmin. (F) S100 immunostaining highlights the presence of nerve bundles and scattered Schwann cells.

the aorta and inferior vena cava and involved the proper hepatic and splenic arteries. The splenic artery was divided using LigaSure devices. The serosa and outer muscular layer and the right vagus nerve at the gastroesophogeal junction were removed. The tumour was dissected so that the adventitia of the proper hepatic artery was carefully separated from the tumour. On completion of the dissection, an 8×5 cm mass was passed off the field, leaving the proper hepatic artery intact from its origin of the coeliac axis as shown in figure 2. The second mass was discovered to have diaphragmatic and pericardial involvement; therefore, a pericardial window was required to complete the dissection. Reconstruction of the central diaphragm with a mesh was required to repair the diaphragmatic defect. Ultimately, a second 8×5 cm mass was removed. In addition, a pyloromyotomy was performed to help improve gastric emptying.

OUTCOME AND FOLLOW-UP

Histopathological examination (figure 3) of both tumours showed similar features composed of proliferation of bland appearing spindle cells with fibroblastoid and focal smooth muscle morphology, fascicular growth pattern and variable collagenous stroma. Focal areas showed prominent myxoid change. Cytological atypia, mitosis or necrosis were not present. The spindle cells were diffusely positive for smooth muscle markers smooth muscle actin (SMA), smooth muscle markers (SMMs), h-caldesmon and desmin. The spindle cells were negative for myogenin, S100, *SOX10*, mdm2, CD34, STAT6, MUC4, HMB45, CD117, DOG1, ER, PR, P16, Ae1/3 and EMA. S-100 and *SOX10* highlighted entrapped nerves and scattered Schwann cells. Ki-67 proliferation index was <2%. Overall, morphological and immunohistochemical findings supported the diagnosis of low-grade smooth muscle neoplasm that failed to meet the diagnosis of leiomyosarcoma. Because of the unusual location and histological features of the tumour, sections were sent to the National Institutes of Health (NIH) for consultation. The NIH characterised this tumour as a myxoid smooth muscle tumour and a hamartoma with a focal Schwannian component having benign features. Next- generation sequencing was negative for reportable gene fusions using the sarcoma-targeted gene fusion panel.

The patient did well postoperatively and was discharged on postoperative day 7. On follow-up, the patient reported improved oral intake without postoperative complications. An MRI to investigate potential metastases discovered a left mandibular mass, an asymmetrical sella turcica and a pituitary mass that was suspicious for pituitary adenoma or Schwannoma. Surgery was performed on the pituitary and this mass was found to be a mucocele.

A next-generation sequencing test targeting analysis of 77 genes associated with hereditary cancer was performed. This revealed the patient to be heterozygous for NM_000051.4:c.3663G>A, a nonsense alteration in exon 24 of the *ATM* gene replacing the tryptophan in position 1221 for a stop codon (NP_000042.3:p.Trp1221Ter). *ATM* is typically associated with the autosomal recessive condition ataxia-telangiectasia, and this variant has been reported in multiple ataxia-telangiectasia patients, although no causal link has been established. The NM_000051.4:c.3663G>A variant is expected to confer a twofold to fourfold increase in female breast cancer and has been associated with an increase in pancreatic and prostate cancer as well.[14 15]

The patient was also heterozygous for EX_13del, a gross deletion spanning exons 13–15 in the *PTCH1* gene. This pathogenic alteration is associated with nevoid basal cell carcinoma syndrome (NBCCS), also known as 'Gorlin syndrome' or 'basal nevus cell syndrome'.[16] This affects approximately every 1 in 310 000 individuals, with over 90% of those individuals developing basal cell carcinoma within their lifetime. In addition, NBCCS can cause odontogenic keratocytes, congenital skeletal abnormalities, cerebral calcifications, macrocephaly, polydactyly, intellectual disability, palmar epidermal pits, and cardiac and ovarian fibromas.[17] Up to 5% of children with NBCCS develop medulloblastoma, also called primitive neuroectodermal tumour. *PTCH1* variants are also found in sporadic cases of medulloblastoma, squamous cell carcinoma, breast cancer and colon cancer. *PTCH1* has also been identified as a rare cause of holoprosencephaly given its role in the Sonic Hedgehog pathway.[17]

Additional variants of unknown significance in this patient included *DICER1* (p.E80K), *RAD51C* (p.A87T) and *RB1*

(p.P23R). Interestingly, the patient later had a mandibular biopsy, which revealed an odontogenic keratocyst commonly found in Gorlin syndrome.

DISCUSSION

Finding a Schwann cell tumour, or any tumour expressing S-100 positivity, in the anterior mediastinum is extremely rare.[18] Tumours of neural crest cell involvement, such as neurofibromas or Schwannomas, are found almost exclusively in the posterior compartment when presenting in the mediastinum, as the posterior compartment is where the majority of the nerves are found.[19–22] Schwann cell hamartomas are not typically positive for smooth muscle stains like SMA, h-caldesmon or desmin.[23 24] One tumour type that is noted to produce peripheral nerve sheath tumours with mixed muscular and nerve histology is a neuromuscular choristoma (NMC). These tumours of developmental aetiology typically present in the first decade of life, although a PubMed search shows at least one case of an oesophageal NMC occurring in a 46-year-old, which stained positive for both desmin and S-100.[25] Schwannomas in the anterior mediastinum are exceedingly rare, with a PubMed search resulting in only three other cases.[26–28] Interestingly, triton tumours, or malignant peripheral nerve sheath tumours with muscular and nervous components, are slightly more common with 13 having been documented in a 2019 literature review.[29] Also, interestingly, these tumours were noted to mostly occur in young men.[29] The age of the patient in this case study at the time of presentation and Marfan's habitus implies a potential embryological or genetic involvement of the disease. The migration of neural crest cells has been linked to other neurogenic gastrointestinal diseases, such as Hirschsprung's disease.[30] Additionally, neural crest cells are known to play a role in the differentiation of smooth muscle cells in the developing embryo.[30 31] Apart from this, cervical neural crest cells in specific somites have been shown to migrate along a posterior retroperitoneal path in the abdomen and involve the oesophageal nerve plexus along their way down.[31 32] It is possible to envision a theory where the presentation of this patient was due to symptoms of improper neural crest cell migration in and around the vagal nerve plexus. However, none of these explanations can account for the mass found in the cardiophrenic region. No embryological theories regarding neural crest cells detail any involvement with the anterior mediastinum.[30]

Learning points

- Hamartomas with Schwannian components are a rare, but potentially debilitating tumour pathology.
- Tumours with Schwannian components are exceedingly rare to find in the anterior mediastinum, and their existence in a patient with Marfan's habitus suggests an unknown genetic component.
- The presence of smooth muscle along Schwannian components in this patient's tumours could lead some credence to the embryological theory that somites migrate with neural crest cells in utero along the vagal nerve plexus.
- This case study presents a unique presentation of a rare tumour, and the genetic analysis of this patient's genome, along with the surgical approach provided, could provide insight to physicians who happen on similar case presentations in their own practice.

Contributors The following authors were responsible for drafting of the text, sourcing and editing of clinical images, investigation results, drawing original diagrams and algorithms, and critical revision for important intellectual content: TJA, FI, JDB, SS. The following authors gave final approval of the manuscript: TJA, FI, JDB, SS.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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