CASE REPORT

De novo 2p16.1 microdeletion with metastatic esophageal adenocarcinoma

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SUMMARY

Microdeletions involving chromosome 2p15-16.1 are a rare genetic abnormality and have been reported in 18 separate patients, mainly children, since 2007. This microdeletion syndrome is characterised by a heterogeneous expression of intellectual impairment, dysmorphic facies, musculoskeletal abnormalities and potential neurodevelopmental anomalies. We report the first case of natural progression in an adult patient who died at a young age of metastatic esophageal adenocarcinoma. Important learning points include the variable phenotypic expression of this microdeletion syndrome and the fact that clinicians must be thorough in investigating objective discrepancies in patients who cannot endorse classical symptoms.

BACKGROUND

The majority of knowledge regarding the chromosome 2p15-16.1 microdeletion syndrome has been described in children. Our aim is to share with clinicians the natural adult history of these patients.

CASE PRESENTATION

A 42-year-old white man presented to our clinic with a 40 pound weight loss over the past 2 years. He lived in a group home and had been on a diet until decreased oral intake, muscle weakness and increasing fatigue became apparent 2 months before his demise. His medical history was significant for intellectual disability and seizure disorder.

The patient had a normal gestation and unremarkable birth, but was noted to have hypotonia at 3 months of age. While he began crawling at 4 months of age, he was unable to sit without support until the age of 9 months. At 18 months, he was noted to have an ataxic gait with outgoing toes. At 3 years age, his vocabulary consisted of 20 words. Cryptorchidism was diagnosed at 9 years. At 10 years, karyotyping was normal, though microcephaly was first documented. He was diagnosed with a seizure disorder at the age of 21, and had been on valproate without further recurrence.

Presently, the patient was noted to be 185 cm tall, with a current weight of 79.3 kg, with a body mass index (BMI) of 23.2. Three years prior, the patient had weighed 97.3 kg (BMI 28.4). Physical examination at the present time revealed elongated facies, eversion of the lower lip vermillion, a thick helix of the ears bilaterally, and a prominent nose without facial asymmetry. He had right esotropia. There was diminished upper extremity muscle tone, and he had proximally placed thumbs. An intention tremor was present bilaterally. His gait was noted to

be mildly spastic, with considerable outgoing of the toes. The patient was able to respond to questioning verbally, but responses were delayed.

His family history was remarkable for a younger sister who had died at the age of 4 from a neuroblastoma. It was not clear if she had a history of intellectual impairment or other similar comorbidities like our patient. His parents and numerous other siblings were otherwise healthy.

INVESTIGATIONS**Genetic analysis**

Array comparative genomic hybridisation (aCGH) revealed an interstitial deletion of 68 oligonucleotide probes spanning ~4.9 Mb at chromosome 2p16.1. Parental fluorescence in situ hybridisation demonstrated that this deletion was not inherited from either parent.

The breakpoints involved for this deletion using Genome Research Consortium assembly 38 (GRCh38) were 55797714-60746979 and included the 5' ends of the *PP4R3B* (protein phosphatase 4 regulatory subunit 3B) and *BCL11A* (B-cell CLL/lymphoma 11A) genes. Table 1 shows the genes involved in our patient's microdeletion, with correlating clinical information.¹⁻⁹

Other studies

MRI of the brain revealed asymmetric lateral ventricles and a prominent cisterna magna without evidence of ventricular obstruction. No other abnormalities were noted. No older MRI was available for comparison.

Given the patient's current presentation, a workup was initiated to evaluate for malignancy or other systemic diseases that could cause the patient's unrelenting weight loss. A CT scan of the chest, abdomen and pelvis revealed numerous liver and bone lytic lesions with diffuse circumferential wall thickening involving the esophagus and stomach in the presence of a hiatal hernia. Follow-up esophagogastroduodenoscopy revealed a friable, ulcerating mass in the distal esophagus with biopsies showing poorly differentiated invasive adenocarcinoma arising in a background of Barrett esophagus with high-grade dysplasia.

OUTCOME AND FOLLOW-UP

As per the family's wishes, the patient was enrolled in hospice and passed away 1 month later.

DISCUSSION

We present a patient with a de novo interstitial deletion of 4.9 Mb on chromosome 2p16.1 who

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Table 1 Genes involved in our patients deletion

Gene	Name	Clinical correlation and comments
<i>PP4R3B</i>	Protein phosphatase 4 regulatory subunit 3B	Involved in DNA repair, but no clinical phenotype or role in cancer pathogenesis reported
<i>PNPT1</i>	Polyribonucleotide nucleotidyltransferase 1	Associated with oxidative phosphorylation defects and deafness; unclear what phenotype haploinsufficiency would present with
<i>EFEMP1</i>	EGF-containing fibulin-like extracellular matrix protein 1	Associated with retinal dystrophy, with homozygotes showing more severe disease; our patient had no recorded eye examination
<i>CCDC85A</i>	Coiled-coil domain containing 85A	No reports in literature
<i>ACTG1P22</i>	Actin γ -1 pseudogene 22	No reports in literature
<i>VRK2</i>	Vaccinia-related kinase 2	Low <i>VRK2</i> mRNA levels have been associated with schizophrenia spectrum disorders
<i>FANCL</i>	Fanconi anaemia complementation group L	Autosomal recessive Fanconi anaemia, with genomic instability and predisposition to cancer due to hypersensitivity to DNA crosslinking agents; unclear if haploinsufficiency of this gene leads to increased cancer risk
<i>EIF3F</i>	Eukaryotic translation initiation factor 3 subunit F pseudogene 3	No reports in literature
<i>IK</i>	<i>IK</i> cytokine	Downregulates HLA-II; unclear if haploinsufficiency of this gene leads to increased cancer risk
<i>BCL11A</i>	B-cell lymphoma 11A	Associated with B-cell lymphomas; haploinsufficiency can cause intellectual disability in animal models

EGF, epidermal growth factor; HLA, human leukocyte antigen.

was diagnosed with metastatic esophageal adenocarcinoma (EAC) at the age of 42. To the best of our knowledge, our case is the first to describe adult mortality in patients diagnosed with this specific deletion. Microdeletions involving the 2p15-2p16.1 were first described in 2007.¹⁰ Since then, there have been 18 more cases reported in the literature.^{11–23} The typical features of this syndrome include dysmorphic facies, microcephaly, developmental delay, intellectual disability, abnormal morphological brain findings, skeletal dysplasia and growth retardation. The majority of cases were described in children, with only two cases being described in adults over the age of 18.

In the initial case report of the 2p15-2p16.1 microdeletion syndrome, Rajcan-Separovic described two non-verbal children with severe dysmorphic facial and musculoskeletal features, including hypotonia in infancy, brachycephaly, bitemporal narrowing, high palate, ptosis, large ears and everted lower lips. Imaging findings of the brain (by MR) included bilateral perisylvian cortical dysplasia and optic nerve hypoplasia.¹⁰ Other imaging findings described in subsequent case reports include leucoplakia, corpus callosum hypoplasia¹⁴ and a simplified cortical gyral pattern.¹⁵ However, other cases reported no brain abnormalities on imaging.^{11 12 15 16} Seizures were described in one case beginning at the age of 12 weeks, and this patient also had numerous renal cysts with nephrocalcinosis.¹⁴

de Leeuw *et al*²¹ described a 32-year-old man born at 42 weeks gestation who had severe psychomotor limitations and growth delay who had a 3.9 Mb deletion involving the 2p15-16.1 coding region. This patient was unable to sit until he was 3.5 years old and did not walk until age 5. Examination of this patient revealed a height of 163 cm, poor speech, a receding forehead, ptosis, telecanthus, retrognathia and widened nipple space, among other distinguishing characteristics. His right testis was absent and his left testis was noted to be small. The patient had multiple renal cysts as well as a dystrophic left kidney seen on ultrasound scan.

Fannemel *et al*¹⁶ reported a 21-year-old man with intellectual deficits noted at age 2 who was found to have a 230 kb deletion the 2p15-16.1 coding region. This patient was 174 cm tall and weighed 52 kg, and his examination revealed a narrow, sloping forehead, ptosis, hypertelorism and retrognathia. An ultrasound scan revealed no abnormalities of his heart or kidneys, and an EEG was normal.

Based on these past reports, this microdeletion syndrome shows great phenotypic variability, and this holds true with our patient. While our patient was noted to have hypotonia in infancy, intellectual disability, microcephaly, facial abnormalities (everted lip, esotropia) and developmental delay, he was mostly verbal and did not show signs of growth retardation. His seizures began at the age of 21 years in contrast to the other report of non-febrile seizures which occurred in infancy. Imaging findings showed asymmetric lateral ventricles and a prominent cisterna magna, but no focal areas of hypoplasia or dysplasia were noted. There were no organ abnormalities noted on intra-abdominal imaging (apart from his metastatic lesions).

aCGH allows for elucidation of the specific genes involved in our patient's deletion. Silencing of the PP4 complex genes may impair repair of DNA replication-mediated breaks,¹ but there is no report specifically identifying *PP4R3B* in cancer pathogenesis or clinical phenotype. *BCL11A* encodes a zinc-finger protein and is well known for its involvement in B-cell lymphomas,^{8 24} and recently, breast cancer,²⁵ but has not been identified for involvement with esophageal cancer. Missense mutations in the N-terminal region of this gene, causing loss of function, have been reported to be associated with intellectual disability and persistence of fetal haemoglobin.⁹ Haploinsufficiency of this gene in mice causes impaired cognition, abnormal social behaviour and microcephaly, which are traits shared by our patient. Unfortunately, we are unable to state if our patient had persistence of fetal haemoglobin. The 5' regions of *PP4R3B* and *BCL11A* were disrupted, but as these two genes are arranged in a head-to-head orientation, a novel fusion protein, which could predispose to cancer, would not be predicted.

The 2p15-16.1 microdeletion syndrome appears to be divided into two groups influenced by the size of the deletion, with one group consisting of larger deletions >3 Mb in length, and the other consisting of shorter, <1 Mb deletions.¹² The phenotype of the larger deletions appear to carry much heterogeneity in clinical appearance, while the smaller deletions appear to report abnormal facies and developmental delay without other defining characteristics such as short stature, autism spectrum disorder, optic nerve hypoplasia or renal abnormalities.^{11 16}

Our patient had a younger sister who died of neuroblastoma at the age of 4, and unfortunately no genomic studies were carried out prior to her demise. As such, it is unclear if there is

a familial cancer predisposition unrelated to our patient's microdeletion, or if germline mosaicism in the parents, resulting in a shared microdeletion, played a role in the cancer pathogenesis of these siblings.

EAC is an uncommon diagnosis, but the incidence has been increasing over the past 50 years. In 2011, the incidence of EAC was 2.5/100 000 in the USA.^{26 27} Furthermore, outcomes from this condition are dismal, with a 5-year mortality of 84% and a median survival of <1 year.²⁶

EAC arises from the premalignant metaplastic changes of Barrett's esophagus (BE) at a rate of about 0.22–0.38% per year.²⁸ Surveillance programmes exist to attempt to decrease the incidence of EAC or catch it at an earlier stage. Various interventions, such as radiofrequency ablation and photodynamic therapy, can be performed on premalignant BE lesions to prevent further progression to malignancy or high-grade dysplasia.

Risk factors for the development of BE include chronic gastroesophageal reflux disease (GERD), age over 50, Caucasian race, visceral obesity (waist circumference >102 cm), current or former smoking, and family history of BE or EAC in a first degree relative. Current American College of Gastroenterology (ACG) guidelines recommend BE screening in patients with a >5-year history of GERD symptoms and at least two other risk factors.²⁹

We report the first known mortality for the 2p16.1 microdeletion syndrome, at a fairly young age with a cancer that must have been present for some time, and was preceded by a premalignant condition. The patient never endorsed reflux symptoms, chest pain, heartburn, brackish taste in the mouth or other gastrointestinal-related symptoms, and it is not clear if he had decreased nociception, was unable to formulate a symptom or was asymptomatic. Felix *et al*¹⁸ described a 4-year-old patient who was diagnosed with GERD at the age of 6 months after the patient was noted to have difficulty gaining weight. However, this does not mirror our patient's clinical course, and no other connection to GERD has been reported.

Learning points

- Our case highlights the phenotypic heterogeneity evident in the 2p15-16.1 microdeletion syndrome.
- We provide the first report of the natural adult history of these patients.
- A high degree of suspicion is needed when caring for patients who cannot share symptoms in expected patterns.

Contributors DCC presented the case history, reviewed the literature, and wrote the first draft of the manuscript. RHG reviewed the genetic breakpoints of the mutation, and edited the manuscript. EGT was the supervising consultant who was the primary provider for the patient and edited the manuscript. All authors participated in the review of the article, reviewed the literature thoroughly and authorised the final manuscript prior to submission.

Competing interests None declared.

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